A. M. A.
AMERICAN JOURNAL OF
DISEASES of CHILDREN

EDITORIAL BOARD

CLIFFORD G. GRULEE, Chief Editor
Box 671, Evanston, Ill.

SAMUEL Z. LEVINE, New York
ROBERT B. LAWSON, Winston-Salem, N. C.
A. A. WEECH, Cincinnati
ROGER L. J. KENNEDY, Rochester, Minn.
FRANCIS SCOTT SMYTH, San Francisco
JAMES L. WILSON, Ann Arbor, Mich.

RICHARD J. PLUNKETT, M.D., Chicago, Managing Editor

MARCH 1951
VOLUME 81 NUMBER 3

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

in the second generation of achievement

For thirty years Dryco has been building up a tradition in infant nutrition. It will be recalled that Dryco introduced vitamin enrichment by irradiation in infant foods. And today the Dryco tradition of excellence is based on maintaining high standards while keeping abreast of progress in nutritional science.

Today, in a second generation, Dryco is proving its usefulness in normal infants...the prematures...the partially breast-fed...the malnourished or convalescent infant...the sick infant. In all these cases Dryco continues to show excellent results in terms of health and growth.

Dryco is easily digested as it forms a soft, flocculent curd of small particle size in the infant's stomach.

An important Dryco advantage is its high-protein and low-fat which minimizes the possibility of digestive upsets caused by excessive fat, while assuring ample protein for satisfying growth.

Dryco is made from spray-dried, pasteurized, superior quality whole and skim milk, providing 2500 U.S.P. units of vitamin A and 400 U.S.P. units of vitamin D per reconstituted quart. Thiamine and riboflavin are preserved largely by the spray-drying process. Only vitamin C need be added. Dryco also supplies more minerals, particularly more calcium, than a corresponding whole-milk formula.

Each tablespoonful supplies 31½ calories. Readily reconstituted in cold or warm water. Available at pharmacies in 1 and 2½ lb. cans.

Write for complete professional literature and samples.

Dryco®

a versatile base for "Custom" formulation

Prescription Products Division

The **Borden** Company, 350 Madison Avenue

New York 17.

Rickets cannot enter . . .

. . . where the SUN never sets

The infant or child who receives Mead's Oleum Percomorphum daily is assured of his supply of vitamin D.

No matter what the clime or season, he lives "in a land where the sun never sets," protected from the shadow of rickets.

Supplying 60,000 vitamin A units and 8,500 vitamin D units per gram, Mead's Oleum Percomorphum provides this dependable prophylaxis in small doses at low cost.

Mead's Oleum Percomorphum comes in bottles of 10 and 50 cc., and of 50 and 250 capsules. Patients appreciate the economy of the large sizes.

Mead's Oleum Percomorphum is the *original* Oleum Percomorphum product—with a background of 17 years of quality and clinical acceptance. Available in all drugstores.

When you prescribe Oleum Percomorphum

Specify

MEAD'S

Oleum Percomorphum

MEAD JOHNSON & CO.

EVANSVILLE 21, IND., U.S.A.

"as the twig is bent"

The foundation for a healthy childhood is largely laid during baby days.

With increased emphasis upon the protein content of baby diets, Strained Tuna BABY FOOD is to be considered as a valuable addition to infant feeding.

Feeding tests and chemical analyses show that fish protein supplies a rich source of amino acids, the essential building blocks of body proteins.

Furthermore, it has been proved that fish protein ranks among those of highest biological value, equivalent to meat or milk protein.*

It also has a high content of fluorine which helps protect against future tooth decay. Contains considerable amounts of the biologically important element, iodine.

And, *babies love it!*

AVERAGE COMPOSITION	
Total Solids	21.8 g
Protein	20.8 g
Fat	0.6 g
Phosphorus	180 mg
Iodine	10 mcg
Fluorine	1.5 mg
Choline	40 mg
Riboflavin	80 mcg
Niacin	12 mg
Animal Protein Factor (B_{12})	8 mcg per 100 grams
(94 calories per 100 grams, or 26.6 calories per ounce)	

ESSENTIAL AMINO ACIDS (Values given as percent of protein)	
Arginine	5.2
Histidine	5.7
Isoleucine	4.7
Leucine	7.0
Lysine	8.3
Methionine	2.8
Phenylalanine	3.5
Threonine	4.1
Tryptophan	1.1
Valine	5.2

Also, a valuable adjunct to many "soft" diets.

VAN CAMP LABORATORIES

Division of Van Camp Sea Food Co., Inc.
Terminal Island, California

*Dunn, M. S.: The Nutritional Value of Fish Proteins, Institute of Food Technologists, San Francisco meeting, (July) 1949. Geiger, E.: Nutritive Value of Fish Protein, Progress in the Chemistry of Organic Natural Products, Ed. by L. Zechmeister, 5:275, 1948.

A request on professional stationery to Dept. ADC will bring samples and bulletins.

"Here Comes What the Doctor Ordered!"

Long before cow's milk lactalbumin allergy was recognized, Goat Milk was used, when available, as a preferred infant food. Today when a change from cow's milk in the diet is indicated, doctors from coast to coast prescribe Meyenberg® Evaporated Goat Milk. It is

1. Uniform in quality.
2. Nutritionally equivalent to evaporated cow's milk.
3. Prepared under exacting conditions by one of the finest condenseries in the west.
4. Available the year round at most drug stores in convenient 14 oz. cans.

Available Without Charge:
Recipe Folder showing how Meyenberg Evaporated Goat Milk can be used in cooking.

By the makers of HI-PRO,® high protein, low-fat powdered cow's milk.

PRODUCTS

Jackson-Mitchell Pharmaceuticals, Inc.

formerly SPECIAL MILK PRODUCTS, Inc.

LOS ANGELES 64, CALIFORNIA • SINCE 1934

How do you score a pediatric constipation corrective?

Check-list for points of consideration which often arise in the selection of a constipation corrective for infants and children.

	CELLOTHYL GRANULES	For your convenience to check other selections	
physiologically correct	☑	☐	☐
produces soft, moist, easy-to-pass stools	☑	☐	☐
gentle in action—no cramping	☑	☐	☐
causes no urgent calls to stool	☑	☐	☐
causes no rebound constipation	☑	☐	☐
not habit-forming	☑	☐	☐
does not interfere with vitamin absorption	☑	☐	☐
does not interfere with digestive process	☑	☐	☐
does not bloat	☑	☐	☐
hypoallergenic	☑	☐	☐
easy to administer	☑	☐	☐

Even the youngest gastrointestinal tract is safe with physiologically correct Cellothyl Granules—designed specifically for use in pediatric practice. Following the normal digestive gradient, Cellothyl provides smooth bulk in the colon. It passes through the stomach and small intestine in a fluid state, then thickens to a smooth gel in the colon, where bulk is needed—encouraging physiologic peristalsis and resulting in soft, formed, easily passed stools.

Easy to administer: Tasteless Cellothyl Granules are simply sprinkled on cereal, fruit or other foods. Children's dosage: ¼ level teaspoon 1 to 3 times daily, depending on age.

Available: Cellothyl Granules in bottles of 25 and 100 Grams. For older children and adults, Cellothyl Tablets (0.5 Gram) in bottles of 50, 100, 500 and 5000.

Cellothyl® brand of methylcellulose especially prepared by the Chilcott Process

GRANULES

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

CHILCOTT
Laboratories DIVISION OF The Maltine Company

MORRIS PLAINS, NEW JERSEY

One Big "NO"

to infant food allergies!

It's a big "NO" to grain allergies when you start babies on Gerber's new hypo-allergenic RICE CEREAL. Contains no yeast. No malt. Low crude fiber (0.3%) and thorough cooking assure high digestibility. Mothers simply add milk or formula and serve!

For variety, alternate with Gerber's other relatively hypo-allergenic cereal—BARLEY. Where no apparent grain allergy exists, Gerber's OATMEAL and CEREAL FOOD (wheat) make extremely satisfactory starting cereals. All have added iron, calcium, B-vitamins.

Samples! Gerber's Cereal "Quads" in miniature sample boxes for your young-mother patients plus Baby Foods Analysis Folder. Write on your letterhead to Gerber's Baby Foods, Dept.263-1, Fremont, Mich.

Babies are our business
...our only business!

Gerber's
BABY FOODS

ACCEPTED
GROWTH IN FOODS AND NUTRITION
AMERICAN MEDICAL ASSOCIATION

SYMPTOMATIC RELIEF

With a high Index of Safety

IN Perennial Allergies

The discomfort caused by year-round allergens such as foods, drugs, feathers, and dust may be relieved by prescribing Neo-Antergan.® Physicians' confidence in Neo-Antergan Maleate, not only for seasonal allergies but also for perennial types, is the result of wide clinical experience with the effectiveness and safety of this antihistaminic agent.

Obtainable only through your prescription, Neo-Antergan is not advertised except to the medical profession.

Your local pharmacy stocks Neo-Antergan Maleate in 25 mg. and 50 mg. coated tablets, in bottles of 100, 500, and 1,000.

NEO-ANTERGAN®

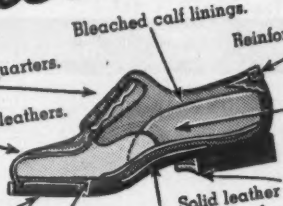
MALEATE

(Brand of Pyrilamine Maleate)
(Formerly called Pyranisamine Maleate)
(N-p-methoxybenzyl-N',N'-dimethyl-N-α-pyridylethylenediamine maleate)

COUNCIL ACCEPTED

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

FLEET-AIR Correctives . . .



. . . the Solution to Most Children's Foot Problems

THIS CUTAWAY VIEW shows clearly why doctors can and do recommend Fleet-Air Correctives for their young patient's foot troubles. The Fleet-Air Corrective line for Children is complete and outstanding in every respect because it has been designed and built to meet specifications set down by leading foot specialists.

Fleet-Air Correctives feature . . . all-leather construction . . . long inside counters . . . reinforced steel shanks and Thomas Heels. A postcard or letter will bring complete details.

Eby Shoe **CORPORATION**
EPHRATA • PENNSYLVANIA

IN UPPER RESPIRATORY INFECTIONS

prompt response

in acute laryngotracheal bronchitis

CASE	DIAGNOSIS	INFECTING ORGANISM	DAYS TREATED	TOTAL DOSE GM.	ADMINISTRATION	CONDITION AND RESULT
16	Acute laryngo-tracheal bronchitis	Hemophilus influenzae	3	12	oral	Marked improve-ment in 24 hours. Recovery

Case report taken from Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Ann. New York Acad. Sc. 53:448 (Sept. 15) 1950.

CRYSTALLINE

Terra

prompt response

in acute follicular tonsillitis

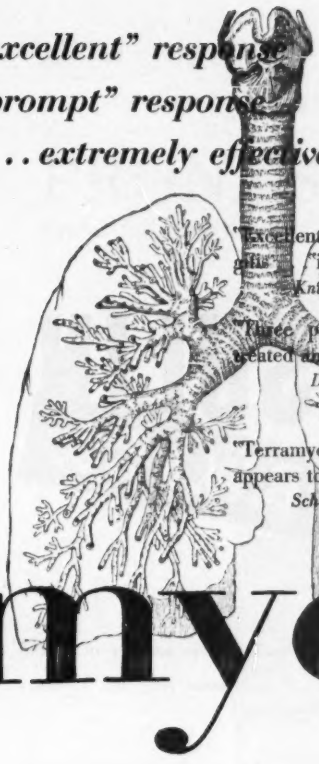
CASE	DIAGNOSIS	CULTURE		DAILY DOSE GM.	NUMBER OF DAYS TREATED	RESULT
		SOURCE	ORGANISM			
29	Acute follicular tonsillitis	throat	Strepto-coccus pyogenes	4	3	Prompt clinical response. No fever after 24 hours of treatment

Case report taken from Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet., Mayo Clin. 25:183 (Apr. 12) 1950.

Antibiotic Division

Pfizer

"excellent" response
"prompt" response
"... extremely effective" *in acute pharyngitis*



"Excellent" results in 3 treated cases of streptococcic pharyngitis . . . "improved promptly following terramycin therapy."
Knight, R.: New York State J. Med. 50:2173 (Sept. 15) 1950.

"Three patients with beta-streptococcic pharyngitis were treated and made a prompt recovery."
Dowling, H. F., Lepper, M. H.; Caldwell, E. R., and Spies, H.: Ann. New York Acad. Sc. 53:433 (Sept.) 1950.

"Terramycin (250 mg. every three hours) when given orally appears to be extremely effective."
Schenck, H. P., Jr. Clin. North America 34:1621 (Nov.) 1950.

mycin

HYDROCHLORIDE

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

Dosage: On the basis of findings obtained in over 150 leading medical research centers, 2 Gm. daily by mouth in divided doses q. 6 h. is suggested for most acute infections. In severe infections a high initial dose (1 Gm.) or higher daily doses (3 to 6 Gm.) should be used. Treatment should be continued for at least 48 hours after the temperature is normal and acute symptoms subside.

Supplied: 250 mg. capsules, bottles of 16 and 100;
100 mg. capsules, bottles of 25 and 100;
50 mg. capsules, bottles of 25 and 100.

CHAS. PFIZER & CO., INC., *Brooklyn 6, N.Y.*

*Intermediate Acting**

GLOBIN INSULIN

'B.W.& CO.'

**Clinical Evidence:—*

"...it was found that the characteristic activity of globin insulin and 2:1 mixture (of protamine zinc and regular) insulin is essentially the same."[1]

"Not often do either globin insulin or a 2:1 mixture require supplementary use of regular insulin. Fully 80% of all severe diabetics can be balanced satisfactorily with one of them."[2]

1. *Roeb, B. B., Rohr, J. H., and Colwell, A. R.: Proc. House Staff Dept. Med., Wesley Memorial Hospital, Chicago, Ill. Feb. 6, 1948.*

2. *Rohr, J. H., and Colwell, A. R., Proc. Amer. Diabetes Assn. 8:37, 1948.*

COMPLETE CLINICAL INFORMATION WILL BE SENT ON REQUEST

'Wellcome' brand Globin Insulin with Zinc, 'B. W. & Co.'®
is supplied in vials of 10 cc., U-40 and U-80

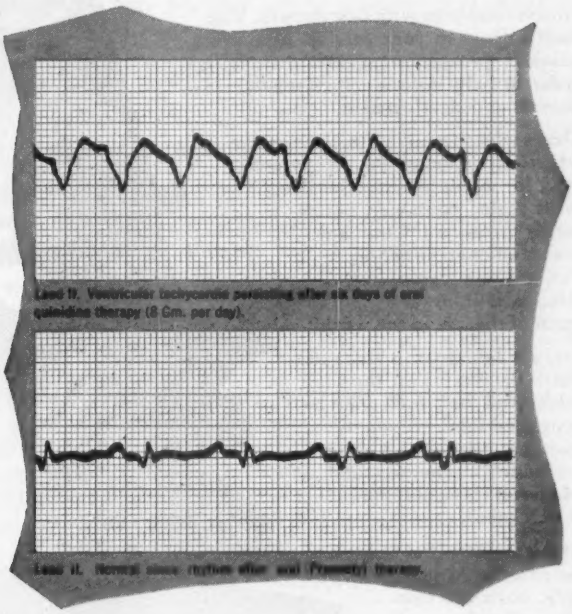
BURROUGHS WELLCOME & CO., (U.S.A.) INC., TUCKAHOE 7, NEW YORK

a new drug . . .

for the treatment of ventricular arrhythmias

PRONESTYL *Hydrochloride*

Squibb Procaine Amide Hydrochloride



Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).

Lead II. Normal sinus rhythm after oral Pronestyl therapy.

Oral administration of Pronestyl in doses of 3-6 grams per day, for periods of time varying from 2 days to 3 months, produced no toxic effects as evidenced by studies of blood count, urine, liver function, blood pressure, and electrocardiogram. Pronestyl may be given intravenously with relative safety.

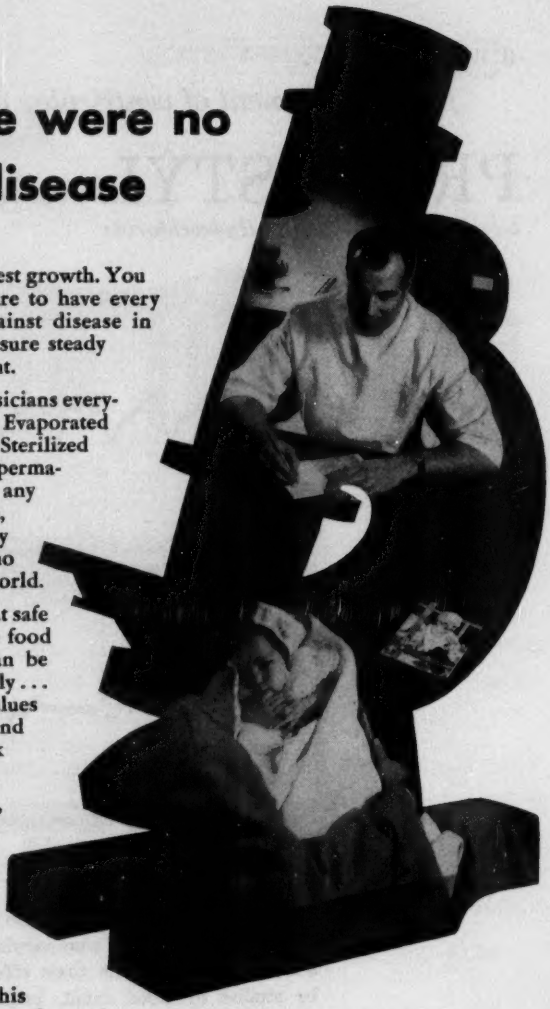
PRONESTYL IS A TRADEMARK OF E. R. SQUIBB & SONS

Pronestyl Hydrochloride Capsules, 0.25 Gm., bottles of 100 and 1000.
Pronestyl Hydrochloride Solution, 100 mg. per cc., 10 cc. vials.

For detailed information on dosage and administration, write for literature or ask your Squibb Professional Service Representative.

SQUIBB MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858.

As if there were no germ of disease



Illness interferes with best growth. You want infants in your care to have every possible protection against disease in order to help maintain sure steady growth and development.

That's why so many physicians everywhere recommend Pet Evaporated Milk for infant formula. Sterilized in its sealed container, permanently protected from any source of contamination, Pet Milk is completely safe, as if there were no germ of disease in the world.

You are assured, too, that safe Pet Milk retains all the food values the best milk can be depended upon to supply . . . and that these food values are uniform wherever and whenever this good milk is purchased.

And it's thrifty! Pet Milk, the original evaporated milk, costs less than any other form of milk . . . far less than special infant feeding preparations!

Try Pet Milk for the babies in your care! Let this safe, low-cost milk help you in your continuous fight against disease!

Favored Form of Milk for Infant Formula

PET MILK COMPANY, 1441-C Arcade Building, St. Louis 1, Missouri

CONTENTS

PAGE

Familial Leukemia: A Report of Leukemia in Five Siblings, with a Brief Review of the Genetic Aspects of This Disease. RAY C. ANDERSON, M.D., PH.D., MINNEAPOLIS 313

Adrenal Cortex Extract in Pediatrics: Possible Effect on the Respiratory System of the Newborn. R. WILLIAM PROVENZANO, M.D.; PHILIP MCGOVERN, M.D.; R. SCHULTZ, M.D., AND JAMES HESTER, M.D., BOSTON 323

Prevention of Minor Skin Irritation (Miliaria) and Impetigo in the Newborn. JEROME GLASER, M.D., ROCHESTER, N. Y.; MARVIN L. THOMPSON, M.D., BERLIN, N. Y., AND THOMAS D. BENSON, M.D., ROCHESTER, N. Y. 329

Adverse Mercurial Reactions in the Form of Acrodynia and Related Conditions. JOSEF WARKANY, M.D., AND DONALD M. HUBBARD, CH.E., CINCINNATI 335

SPECIAL ARTICLE:

The American Journal of Diseases of Children. CLIFFORD G. GRULEE, M.D., EVANSTON, ILL. 374

CASE REPORTS:

Cleidocranial Dysostosis Syndrome: Report of a Case in a Negro Child Exhibiting Retarded Growth. ROLAND B. SCOTT, M.D., AND L. OTTO BANKS, M.D., WASHINGTON, D. C. 394

Dermatomyositis with Nephritis in a Negro Girl. J. EDMUND BRADLEY, M.D.; MILES E. DRAKE, M.D., AND H. PATTERSON MACK, M.D., BALTIMORE 403

PROGRESS IN PEDIATRICS:

Mixed Tumor of the Liver: Report of a Case with a Review of the Literature. DORIS H. MILMAN, M.D., AND DAVID M. GRAYZEL, M.D., PH.D., BROOKLYN 408

ABSTRACTS FROM CURRENT LITERATURE 421

SOCIETY TRANSACTIONS:

Chicago Pediatric Society 453

NEWS AND COMMENT 460

OBITUARIES:

Leonard Parsons, M.D. 461

BOOK REVIEWS 463

THE A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN is published by the American Medical Association as a medium for the advancement of knowledge of the diseases of children and for the publication of scientific investigation in this field.

Communications regarding subscriptions, reprints, etc., should be addressed, A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN, American Medical Association, 535 North Dearborn Street, Chicago 10.

Manuscripts for publication, books for review and correspondence relating to contributions should be sent to Dr. Clifford G. Grulee, Chief Editor, Box 672, Evanston, Ill., or to any other member of the Editorial Board.

Articles are accepted for publication on condition that they are contributed solely to the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

Matter appearing in the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN is covered by copyright but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN or in any of the other publications issued by the Association will not be permitted.

THE A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN is published monthly. The annual subscription price (for two volumes) is as follows: domestic, $12.00; Canadian, $12.40; foreign, $13.50, including postage. Current single copies are $1.25, postpaid.

Checks, money orders and drafts should be made payable to the American Medical Association.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (three volumes): domestic, $15.00; Canadian, $16.50; foreign, $19.00. Single copies, 45 cents.

A. M. A. ARCHIVES OF INTERNAL MEDICINE—Monthly. Devoted to the publication of advanced original clinical and laboratory investigations in internal medicine. Illustrated. Annual subscription price (two volumes): domestic, $10.00; Canadian, $10.40; foreign, $11.00. Single copies, $1.00.

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): domestic, $14.00; Canadian, $14.40; foreign, $15.50. Single copies, $1.25, except special numbers.

A. M. A. ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, annual reviews of special subjects, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, $1.00, except special issues.

A. M. A. ARCHIVES OF INDUSTRIAL HYGIENE AND OCCUPATIONAL MEDICINE—Monthly. Devoted to the advancement of knowledge of the diseases of industry and to the publication of scientific investigation in this field. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00, including postage. Single copies, $1.00.

QUARTERLY CUMULATIVE INDEX MEDICUS—A complete subject and author index to the worth while current medical literature of the world. Issued twice a year. Volumes bound for permanent reference. Subscription price, calendar year: domestic, $20.00; Canadian, $22.00; foreign, $22.00.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **CHICAGO 10**

A. M. A.
American Journal of Diseases of Children

VOLUME 81 MARCH 1951 NUMBER 3

COPYRIGHT, 1951, BY THE AMERICAN MEDICAL ASSOCIATION

FAMILIAL LEUKEMIA

A Report of Leukemia in Five Siblings, with a Brief Review of the Genetic Aspects of This Disease

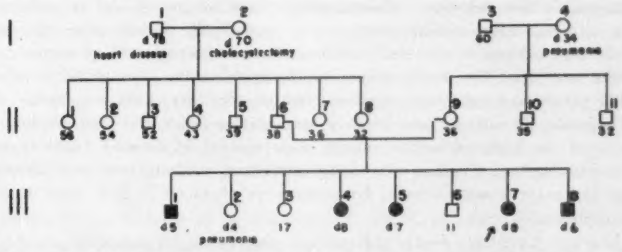
RAY C. ANDERSON, M.D., Ph.D.
MINNEAPOLIS

THE OCCURRENCE of multiple cases of leukemia within a single family has often been sufficiently striking to merit a published report by the clinician who encountered it. An excellent review of such cases has been made by Videbaek,[1] who has summarized 26 "incontrovertible" cases in the literature up to 1947 and has added 13 cases of his own.

The family to be described in the present report is unique in several respects. It is the first reported with leukemia in more than three siblings, and it represents an easily studied group, for all affected members have been examined and treated in the University of Minnesota Hospitals within the last 14 years.

CLINICAL MATERIAL

The pedigree of the "S." family is shown in the figure. Only the near relatives are included, and the affected persons are indicated by solid symbols. There have been no consanguineous



Pedigree of the "S." family, including only the near relatives. Persons with leukemia are indicated by the solid symbols. Kindred K 215, Dight Institute.

marriages. This pedigree has not been reported in any previous studies, except for the inclusion of the first affected sibling in a survey [2] of leukemic cases which had been seen in the pediatric services of University Hospital from 1930 to 1938. It is indeed ironical that at that time this sibling fitted into the group with negative family histories!

From the Dight Institute for Human Genetics and the Department of Pediatrics, University of Minnesota.

1. Videbaek, A.: Heredity in Human Leukemia and Its Relation to Cancer (Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis), Copenhagen, Ejnar Munksgaard Forlag, 1947, vol. 13.

2. Booth, M., and Rembolt, R.: Leukemia in Childhood: Evaluation of Present Status of Problem with Particular Reference to Study of Cases Treated at the University of Minnesota Hospitals from 1930 to 1938, Journal Lancet **59**:216-229, 1939.

REPORT OF CASES

SIBLING 1 (J. S.).—This 5 year old white boy was admitted to the University Hospital on Feb. 28, 1936, with the complaint of swelling of the right leg of three weeks' duration. There had been no fever or pain, and only temporary relief had been obtained from elevation of the leg and heat applications. Birth and development had been normal, and the child had had mumps, chickenpox, measles, frequent infections of the upper respiratory tract and numerous nosebleeds. The boy was noted to be well developed on physical examination. A perforation of the right ear tympanic membrane was observed, as well as carious teeth, enlarged tonsils, mildly inflamed pharynx and shotty cervical and axillary lymphadenopathy. A systolic murmur was present, and the right leg was moderately swollen. Blood pressure values in the two legs were normal and equal; the pulses in the dorsalis pedis arteries were easily palpable, and the affected leg showed no evidence of infection. Blood culture was negative for pathogens. Urinalysis gave normal results. The Wassermann reaction was negative, and blood studies showed a hemoglobin concentration of 78 per cent, 7,800 leukocytes and a differential count of 18 per cent neutrophils, 79 per cent lymphocytes (described as "atypical"), 2 per cent monocytes and 1 per cent eosinophils. Roentgenograms of the pelvis and leg bones were considered normal. The patient had a low grade fever for five days and was discharged on March 16 without a definite diagnosis.

The patient was seen again on May 8, at which time pitting edema of the right leg was noted.

On July 7 the patient was admitted to the hospital with numerous complaints. Bleeding from the gums had developed following a tooth extraction on June 26. A week later he had fallen from a tree, resulting in a painful right shoulder. Soon thereafter recurrent nosebleeds, hematemesis, dark stools, ecchymoses, fever, mild jaundice and weakness developed. Physical examination revealed a weak, apathetic, extremely ill boy with decided pallor and a temperature of 103 F. The skin had an icteric tinge, and a large tender subcutaneous swelling was present over the right side of the chest. Petechiae were noted on the right tympanum, and there was an ecchymosis on the arm. The right leg was more swollen than on the previous admission. Blood studies showed a hemoglobin concentration of 20 per cent, 690,000 red blood cells and 1,900 leukocytes, with a differential count of 46 per cent neutrophils and 54 per cent lymphocytes. Bleeding and clotting times were normal, and 50,000 thrombocytes (platelets) were present. Roentgenograms of the skull and long bones were reported as normal. Repeated blood studies were done, but no diagnosis could be made on the basis of the peripheral blood smear. The patient had numerous petechiae, hematemesis, tarry stools and marked fever, and despite transfusion therapy he lapsed into a semicomatose state and died on July 17, 1936. Examination of the bone marrow at autopsy was reported as showing "marked decrease in number of granulocytes. There is a moderate number of nucleated red cells present. There is a large excess of immature cells, lymphocytic in character." The final diagnosis was lymphatic aleukemia.

SIBLING 4 (L. S.).—This 8 year old girl was admitted to University Hospital on June 1, 1942, with complaints of pain in the neck and fever. In April she had had an episode of tonsillitis, which had responded to sulfapyridine therapy. After this, she remained somewhat pale and listless, however, and in May there was a return of pain in the neck, cervical adenitis and fever. During the previous winter the girl had had pneumonia and in earlier years measles, chickenpox and mumps. Otherwise, her development had been normal.

Physical examination revealed an acutely ill child whose temperature was 100.2 F. The skin had a pale yellow tinge, and there was a small ecchymosis on the lower part of the left leg. Submental, posterior cervical and submaxillary lymph nodes were prominent, but only small inguinal nodes and no axillary nodes were palpable. Both fundi showed papilledema and hemorrhages. The mucous membranes were pale, the teeth carious and the tonsils small, and there was a soft systolic murmur along the left sternal border. Initial blood studies showed a hemoglobin concentration of 2.74 Gm. and 3,450 leukocytes, with a differential count of 59 per cent neutrophils, 39 per cent lymphocytes and 2 per cent myelocytes and a thrombocyte count of 110,000. Wassermann and tuberculin reactions were negative; blood cultures were sterile, and urinalysis gave normal findings. The patient acquired lobar pneumonia and was

treated with numerous blood transfusions, sulfadiazine and various iron and vitamin preparations. Roentgenograms of the chest were indicative of lobar pneumonia, and sinus films demonstrated bilateral ethmoid and maxillary sinusitis. The bone marrow on June 16 was interpreted as "markedly hypoplastic (almost aplastic) with all cell lines equally affected. The great increase in lymphocytes appears to be on a relative basis and does not seem to indicate a leukemic change." The bone marrow on a repeat examination one month later was also reported as hypoplastic. The patient was discharged on July 31, 1942, with a diagnosis of lobar pneumonia and idiopathic hypoplastic anemia.

Two weeks later the patient was again hospitalized because of weakness and poor appetite. She appeared fairly well nourished and was in no acute distress but had a temperature of 101.2 F. A soft diastolic murmur was now present over the entire precordium. Blood studies showed a hemoglobin concentration of 4.07 Gm., 2,850 leukocytes and a differential count of 55 per cent neutrophils and 45 per cent lymphocytes. Blood cultures were sterile. The patient had a high fever; the liver and spleen became palpable; purpuric spots appeared, and bronchopneumonia developed. The peripheral blood and bone marrow on October 14 were interpreted as showing "lymphatic leukemia, partially differentiated." Roentgenograms of the pelvis showed probable leukemic infiltration. An electrocardiogram indicated myocardial damage, and biopsy specimens of the skin lesions were suggestive of leukemic infiltration. Repeated transfusions were given, as well as sulfadiazine, but the patient's condition rapidly deteriorated, and she died on Nov. 1, 1942. Autopsy observations confirmed the diagnosis of lymphatic leukemia.

Sibling 5 (R. S.).—This 4 year old girl was admitted to University Hospital on Jan. 14, 1942, because of dyspnea and fever. A "cold" in late December had developed into pneumonia which failed to respond to treatment with one of the sulfonamides. Except for measles, chickenpox and whooping cough, the girl's earlier development had been uneventful.

Physical examination showed a pale, acutely ill girl with rapid respiration and a temperature of 104.2 F. The posterior cervical lymph nodes were enlarged; the left ear drum was moderately inflamed, and the pharynx was diffusely injected. The right side of the chest showed decreased respiratory movements, dulness and diminished breath sounds. Blood studies revealed 5.8 Gm. of hemoglobin, 1,520,000 red blood cells, 4,650 leukocytes and a differential count of 16 per cent neutrophils, 82 per cent lymphocytes and 7 per cent monocytes. The blood Wassermann reaction was negative, and examination of the urine and spinal fluid gave normal results. Chest roentgenograms confirmed the clinical impression of empyema, and cultures showed the infecting organisms to be type 5 Pneumococcus and Staphylococcus. The patient was treated with transfusions and sulfadiazine, as well as aspiration and surgical drainage of the chest. During the prolonged period of hospitalization furunculosis and otitis media also developed. The chest condition finally cleared, and the patient was discharged on July 31, 1942.

The patient was then followed in the pediatric outpatient clinic because of the recent empyema and the incidence of leukemia in the family. Approximately a dozen visits were made to the clinic during the next two years, the patient being treated for skin abscesses and for eye and ear complaints. Repeated blood studies were done, with the hemoglobin concentration varying from 9.5 to 11.5 Gm., the red blood cell count hovering around 3,000,000, the leukocyte count varying from 3,000 to 4,650 and the thrombocyte count ranging from 120,000 to 160,000.

In February 1944 the patient suffered an attack of "flu" and subsequently experienced repeated nosebleeds. However, there were no striking clinical findings at this time. No adenopathy was noted and the spleen and liver could not be felt. The blood showed toxic neutrophils but no immaturity.

During the next month the nosebleeds continued to occur, and the patient displayed anorexia, fatigue and weight loss. When seen on April 22, 1944 in the clinic, the patient had a markedly different appearance, in both clinical and laboratory findings, and she was, therefore, admitted to the hospital. She now appeared thin and chronically ill, with sallow yellowish skin and petechiae and ecchymoses on the trunk and extremities. The teeth were carious. There was a slight decrease in breath sounds in the right base of the chest posteriorly,

and a soft systolic murmur could be heard at the cardiac apex. Blood studies showed a hemoglobin concentration of 6.6 Gm., 1,970,000 red blood cells, 55,150 leukocytes, a differential count of 8 per cent neutrophils, 10 per cent lymphocytes, 80 per cent blast cells and 2 per cent eosinophils and thrombocyte count of 60,000. Blood cultures were sterile. Bone marrow examination showed poorly differentiated lymphatic leukemia. The patient had a spiking fever, nosebleeds, otitis media and pyodermas, and she was treated with transfusions and penicillin. The liver and spleen became palpable, and lymphadenopathy developed. Despite transfusions, the hemoglobin value hovered at 3 to 4 Gm. and the leukocyte count rose to 137,000, with 98 per cent immature lymphocytes. The patient died on July 23, 1944. Pertinent autopsy observations included leukemic infiltrations in the skin, myocardium, lungs, liver, bowel, spleen, kidneys and lymph nodes, as well as the bone marrow. The final diagnosis was lymphatic leukemia.

SIBLING 7 (B. S.).—This 8 year old girl was admitted to the University Hospital on Feb. 16, 1949. In January she had suffered from a "cold" which had then progressed to purulent otitis media. This was treated with penicillin at a community hospital. A routine blood smear was interpreted as showing leukemia, and the patient was then referred to University Hospital for further study. The patient gave a history of prolonged "colds" each winter, usually complicated by earaches. During the previous three years she had been receiving "tonic" to build up her blood. She had had none of the usual childhood illnesses, and she had always been "peppy."

Physical examination showed a small, thin girl with pale waxy skin and sallow complexion who was alert and not acutely ill. The left tympanic membrane was retracted: the fundi and mucous membranes were pale; the teeth were carious, and there was minimal enlargement of the cervical and inguinal nodes. A soft systolic murmur could be heard at the apex of the heart. The spleen and liver both projected several inches below the costal margins. The Wassermann reaction was negative, and urinalysis gave normal findings. Blood studies showed 6.2 Gm. of hemoglobin, 2,000,000 red blood cells, 9,060 leukocytes, 2.3 per cent reticulocytes and a differential count of 11 per cent mature neutrophils, 1 per cent mature eosinophils, 28 per cent mature lymphocytes, 13 per cent mature neutrophils, 2 per cent immature eosinophils, 8 per cent immature lymphocytes, 13 per cent monocytoid cells and 24 per cent blast forms. The patient was discharged a week later, after having received a number of transfusions.

She was readmitted on March 14 for consideration of Aminopterin (4-aminopteroylglutamic acid) therapy. Bone marrow examination at this time was interpreted as indicating leukemic reticuloendotheliosis. The patient was then treated with Aminopterin (two courses, each consisting of 0.5 mg. daily for 14 days). She had purulent otitis media while hospitalized and was treated with sulfadiazine and penicillin. Transfusions were also given. She was discharged on May 7, receiving 1.0 mg. of Aminopterin weekly.

One month later examination disclosed her physical condition to be much the same, but her blood now showed 5.2 Gm. of hemoglobin, 18,500 leukocytes (with 39 per cent immature granulocytes or blast cells) and 218,000 thrombocytes. In July the patient appeared weaker and chronically ill. A few petechiae were noted on her left cheek. Blood studies showed 4.4 Gm. of hemoglobin, 7,650 leukocytes (with 27 per cent blast or immature cells) and 106,000 thrombocytes. As on the June visit she was given transfusions, and Aminopterin therapy was continued.

On her next visit, August 17, the clinical and laboratory findings were essentially unchanged, except that the thrombocyte count had now dropped to 70,000. She was given several transfusions, and Aminopterin therapy was discontinued. Five days later she was readmitted to the hospital with complaints of cough, dyspnea and fever. She appeared acutely ill, with a temperature of 103 F., a pulse rate of 120 and a respiratory rate of 40. She was dyspneic and showed alar flaring and expiratory grunting. Rales were heard in the chest bilaterally, but no dulness was noted. Chest roentgenograms showed bilateral lung changes compatible with either leukemic infiltration or bronchopneumonia, or both. The patient was given penicillin and oxygen, and after a brief stormy episode of cyanosis and stupor she improved sufficiently to justify discharge on September 1. At this time her chest still contained coarse rales, and her leukocyte count was 23,850. She was discharged receiving aureomycin therapy and got

along fairly well for about 10 days. Weakness then developed, and she died at home on Sept. 13, 1949. Circumstances prevented an autopsy from being carried out. The final diagnosis was leukemic reticuloendotheliosis (primarily myelogenous) and bronchopneumonia.

SIBLING 8 (R. S.).—At the time the present study was started this boy was included as one of the nonaffected siblings. In March 1949 his blood was studied, and the routine tests showed 12.3 Gm. of hemoglobin, 7,750 leukocytes and a differential count of 20 per cent neutrophils, 76 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. In August 1949 the findings were 11.2 Gm. of hemoglobin, 5,700 leukocytes and a differential count of 11 per cent neutrophils, 81 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils; the cells were considered to be morphologically normal by the examining hematologist. At this time, the boy was checked physically and the medical history was reviewed. He had never had any of the childhood illnesses and had never received medicaments of any type. Positive physical findings were limited to carious teeth. There was nothing to suggest either incipient or impending disease.

He was next seen in the pediatric clinic on April 6, 1950, having been referred to the hospital because of severe anemia. In January he had had otitis media, from which he recovered in two weeks. Several weeks later he acquired measles, complicated by encephalitic symptoms. He was then well until March 28, when earaches and fever recurred. These symptoms responded to sulfonamide therapy temporarily, but several days later the fever returned. The patient was hospitalized in his community hospital for penicillin therapy, and at that time the hemoglobin concentration was found to be 5.9 Gm.

Examination at the University Hospital on April 6 showed a well developed and well nourished boy 6 years of age. He had a sallow complexion but was in no acute distress. The teeth were noted to be in poor condition, and adenopathy was palpable in the cervical, epitrochlear, axillary and inguinal regions. There was a systolic murmur audible along the left sternal border and over the aortic area. The liver was felt several centimeters below the costal margin, and the spleen was questionably palpable. Urinalysis gave normal results. Blood studies showed a hemoglobin concentration of 5.1 Gm., 2,010,000 red blood cells, 4,050 leukocytes, a differential count of 26 per cent neutrophils, 78 per cent lymphocytes, 2 per cent monocytes and 4 per cent eosinophils and a thrombocyte count of 112,000. The sedimentation rate was 147 mm. in one hour. The bone marrow and peripheral blood were examined by a hematologist, who considered the marrow smears inadequate, yet suggestive of possible leukemic reticuloendotheliosis.

The patient was hospitalized in University Hospital for five days in late April. Physical findings were about the same as on previous examinations. Blood studies showed 4.4 Gm. of hemoglobin and 3,300 leukocytes. Bone marrow smears were reported as displaying no change from the earlier smears. He was transfused and was discharged with a hemoglobin value of 13.1 Gm.

His next admission was on June 3, at which time he gave a history of a spiking fever of three days' duration. He now appeared pale but not acutely ill, despite a rectal temperature of 103 F. Scattered rhonchi were noted in the chest; a soft apical systolic murmur was present, and the tip of the spleen could be felt several centimeters below the costal margin on the left. His blood showed 2,550 leukocytes, with a differential count of 80 per cent lymphocytes, 16 per cent neutrophils and 4 per cent basophils. Urinalysis gave normal findings. Repeated chest roentgenograms were interpreted as normal. The patient continued to have a spiking fever until June 10. Results of bone marrow and peripheral blood examinations at about this time were interpreted as compatible with a diagnosis of leukemia, and therapy with pituitary adrenocorticotropic hormone (ACTH) was started. Ten milligrams was given every six hours for a total dose of 120 mg., after which the boy was considered to have improved clinically. Blood studies on June 19 showed 11.7 Gm. of hemoglobin, 7,150 leukocytes and 54,000 thrombocytes. The bone marrow on June 20 showed hyperplastic changes, although the peripheral blood and marrow were still interpreted as leukemic. The patient was discharged on June 22, 1950, at which time he had several inconspicuous papules on the forehead.

On the following day he complained of abdominal pain and leg pain. A generalized eruption of vascular lesions developed, but he remained afebrile. During the evening of the following

day he had three convulsions, followed by persistent epistaxis. He was admitted again to the hospital on June 25. He appeared restless and had a rectal temperature of 101 F. and a pulse rate of 104. He was covered by vesiculobullous eruption which extended to the palms and soles and included the mucous membranes. There was minimal bleeding from the right nostril. The liver and spleen were both easily palpable. Spinal fluid examination gave normal findings. Cultures of the blood and spinal fluid were sterile. In view of a history of exposure to chickenpox in early June, the eruption was considered to be that of chickenpox.

The patient continued to show bleeding from the nose and gums, and the vesicles became hemorrhagic. The patient gradually became weaker, concomitant with a fall in temperature, and died on the day following admission. Blood studies on the day of death showed 49,000 thrombocytes, 12.3 Gm. of hemoglobin and 120 normoblasts per 100 leukocytes. Autopsy observations were compatible with the diagnoses of leukemia and chickenpox.

In addition to these five children with verified leukemia, one other sibling presented interesting blood findings and is, therefore, being reported on in detail.

SIBLING 2 (A. S.).—This 4 year old girl was admitted to University Hospital on April 30, 1940, with complaints of cough and fever. Six weeks prior to admission she had had bronchitis, but a roentgenogram of the chest had been reported as normal. The cough continued, and one week before admission she had a high fever. The child's past health had been good, and she had suffered only measles and chickenpox.

On physical examination the girl appeared pale and chronically ill. The nasal turbinates were pale and swollen; the teeth were carious, and the tonsils were enlarged and injected. There was lagging of the lower right side of the chest on respiration, as well as dulness to percussion and suppressed breath sounds over the same area. Admission blood studies showed a hemoglobin concentration of 44 per cent, 2,190,000 red blood cells, 21,600 leukoctyes and a differential count of 32 per cent neutrophils, 23 per cent lymphocytes, 33 per cent monocytes, 1 per cent basophils and 4 per cent immature granulocytes. Chest roentgenograms showed an encapsulated effusion in the right side of the chest. Because several routine differential counts were reported as showing cell immaturity, a bone marrow examination was made, with the pathologist reporting "some immaturity—toxic changes—in all probability leukemoid, marrow, hyperplastic, actively regenerative, with no evidence of leukemia." The patient was treated with sulfapyridine, thoracentesis and transfusions and was discharged on May 18, 1940 in an improved condition.

Two months later she was readmitted because of stridor, hoarseness and a brassy cough. These were noted on physical examination, as well as decreased resonance and breath sounds over the right lower part of the chest and wheezes throughout both pulmonary fields. A chest roentgenogram was interpreted as being consistent with a diagnosis of bronchitis. At this time, the hemoglobin concentration was 53 per cent and the leukocyte count 5,300. The bone marrow and peripheral blood were again examined by a hematologist, who reported that the peripheral blood showed toxic changes, but no immaturity, and that the marrow was regenerative, with no evidence of leukemia. The child died four days after admission, shortly after bronchoscopy and tracheotomy had been performed. Autopsy revealed findings indicative of pneumonia, tracheitis and bronchitis, but no evidence of leukemia. However, autopsy records failed to show whether or not the bone marrow and lymph nodes had been examined.

STUDY OF NORMAL SIBLINGS AND PARENTS

In 1944, during the illness of sibling 5 (R. S.), blood studies with normal findings were reported to have been done on the surviving members of the sibship, which would thus include siblings 7 and 8, who subsequently had leukemia. However, these findings were not placed on permanent record. In March 1949 routine blood studies were done on the three nonaffected siblings. Later, after I had become interested in this family, blood studies were repeated on these siblings,

as well as on the parents. Also, at this time (August 1949), the medical histories of the three siblings were reviewed and physical examinations were carried out on them. The oldest sibling (sibling 3, M. S.) had always been in good health. As a child she had had scarlet fever, measles, chickenpox and mumps, all without sequelae. She had had numerous sore throats and ear infections and had been given sulfonamides on at least one occasion. The only significant physical findings were carious teeth and greatly enlarged tonsils. Sibling 6 (J. S.) had enjoyed excellent health and had had only measles and chickenpox. He had never received any medicaments. Physical examination showed numerous carious teeth, but he was otherwise in good physical condition. The findings on sibling 8 (R. S.), who at that time was apparently normal but who subsequently had leukemia, have already been described.

The results of the blood studies on the above siblings and on the parents are shown in the table. The cells were considered to be morphologically normal by the examining hematologist.

Results of Blood Studies

	Sibling 3		Sibling 6		Mother (II 9)	Father (II 6)
Age and sex	16	F	10	M	36	38
Dates (1949)	March	Aug.	March	Aug.	Aug.	Aug.
Hemoglobin, Gm./100 cc.	13.1	13.9	13.0	13.9	14.4	15.9
Leukocytes/cu. mm.	9,950	5,200	5,400	6,000	8,200	6,550
Differential Count, %						
Neutrophils	68	46	34	35	71	54
Lymphocytes	28	47	60	51	26	37
Monocytes	2	3	2	5	2	5
Eosinophils	1	4	4	9	1	4
Basophils	1	0	0	0	0	0

COMMENT

A study of a single family cannot be expected to throw much light on the relative importance of genetic factors in leukemia. In fact, the general tendency in medicine to report only families in which numerous members are affected contributes a bias which is often overlooked by the person who "reviews the literature." Nevertheless, the occurrence of multiple cases in siblings provides an opportunity to study the disease in closely related persons with respect to type of disease, early symptoms and physical findings. Because of a greater uniformity in both the physical and the genetic environment, one can generally expect the manifestations of a disease to be more uniform among multiple cases in a family than among cases in the general population. In the present family perhaps the most striking feature has been the similarity in age of onset of leukemia in the affected children (ages 5 to 8). Videbaek [1] emphasized the tendency for leukemia to appear at about the same age in siblings, although practically all his data related to adult siblings. Only one of the familial cases cited by him, that reported by Jelke, involved more than one child, and this concerned monozygous twins who had leukemia at 4 and 5 months of age. (Since Videbaek's study, Riel [3] has

3. Riel, L.: Akute lymphatische Leukämie bei (eineiigen) Zwillingen, Kinderärztl. Prax. **16**:148-151, 1948.

reported leukemia in monozygous twins, both of whom died at the age of 3 years.) In seven other families there were one affected child and one or more affected adults. The uniform age of onset in the present family speaks for a strong genetic factor. One expects this type of appearance to occur in hereditary diseases due to rare but highly penetrant recessive genes. Balancing this similarity, however, is the variable expression of the disease with respect to clinical findings in the various persons.

That there is a genetic factor in leukemia seems quite well substantiated, despite the fact that cases are generally sporadic in occurrence. Such workers and reviewers as Ardashnikov,[4] Snyder,[5] Gates[6] and Videbaek[1] have favored the idea that leukemia may be due to a dominant gene with low penetrance. If this is true, only a small fraction of persons carrying the gene will exhibit the disease, thereby masking the hereditary aspect of the disease. Brandberg[7] and others felt, however, that the genetic factor is generally of little significance, and Forkner[8] included heredity among the factors whose "relationship probably is incidental and by no means is certain."

Videbaek examined the families of 209 leukemic patients and found that 17 (8.1 per cent) of them contained other affected members. Although earlier authors had suggested that familial cases were almost always of the lymphatic type, Videbaek noted a general distribution. His analysis of the 39 known cases of familial leukemia showed that in 17 families only one type of leukemia was present and in 22 families more than one type. These facts led him to conclude that "the hereditary factors susceptible of operating in the etiology of leukemia are common, or the same, for all the different varieties of the disease," a view also hinted at by Ardashnikov. Such analyses must be viewed with caution, however, in view of the considerable difficulty involved in the exact classification of the leukemias, as well as the lack of uniformity among pathologists in the terminology. Thus, in the family reported on in the present paper, several different diagnoses—lymphatic aleukemia, lymphatic leukemia, reticuloendotheliosis—are listed, although the disorders are all considered to be closely related by the pathologist familiar with the cases.

In hereditary diseases involving dominant or recessive genes with low penetrance, one attempts to identify those factors which modify the threshold at which the disease will make its appearance and those factors that influence the appearance of the disease. These factors may be genetic (modifying genes) or environmental (infections, trauma, etc.). In the present family one is impressed by the frequency of carious teeth, respiratory infections and sulfonamide medications. However, it is impossible at present to determine the importance of such "precipitating factors," and one must of necessity be careful in ascribing etiological significance to them. Along this line, it is important to point out that the normal siblings in the family have also been subject to most of the same environmental factors. In

4. Ardashnikov, S. N.: Genetics of Leukemia in Man, J. Hyg. **37**:286-302, 1937.

5. Snyder, L. H.: The Principles of Heredity, ed. 3, Boston, D. C. Heath & Co., 1946.

6. Gates, R. R.: Human Genetics, New York, The Macmillan Company, 1946.

7. Brandberg, O.: Studien über das klinische Bild der Leukosen und der sog. leukämoiden Reaktionen im Kindesalter, Acta pædiat. (supp. 1) **30**:1-286, 1943.

8. Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938.

reviewing the environmental background of this family, an attempt was made to identify possible causal factors. However, living conditions were apparently identical with those of the general population. The family had lived in the same small town continually but had moved from one end of the town to the other about seven years ago.

Numerous reports have dealt with the possible association of leukemia with cancer in general, with pernicious anemia and with leukocytosis. Thus, Videbaek, as well as Gross and Matte,[9] reported an increased frequency of malignant tumors among relatives of leukemic persons, as compared with the incidence in relatives of normal controls. Busk[10] has criticized some of Videbaek's calculations, although he still noted increased cancer risks for fathers and sisters of leukemic patients. Gorer[11] found fault with Videbaek's choice of controls and was highly critical of any suggestions that nonspecific predispositions to cancer occur in human beings. Gorer also objected to the idea of postulating single genes as the determining factor in malignant disease and stated that most pathological conditions appear to "depend upon a number of genes differing greatly in effect in different environments. Videbaek has obtained evidence that some fairly effective genes are not uncommon in Denmark, so far as leukaemia is concerned."

With respect to the association of leukemia and pernicious anemia, few reliable data are available, other than that of Videbaek (8.1 per cent of leukemic patients had relatives with pernicious anemia), who concluded that

> It is not possible to say anything certain about the nature of the relation between pernicious anemia and leukemia, but it lies near to conceive it as due to a hereditary factor of importance for the functioning of the hemopoietic tissue, perhaps for its capacity for differentiation, favoring the development now of leukemia, now of pernicious anemia. The relationship may perhaps be due to a hereditary disposition which leukemia and pernicious anemia have in common with cancer.

Numerous cases of leukemia and pernicious anemia in the same person have been reported in the literature, with sometimes leukemia and sometimes pernicious anemia appearing first.

The third postulated association, that of leukemia and leukocytosis, is more pertinent to the family described in this paper. Assuming that some persons predisposed to leukemia may instead reveal their "hereditary taint" by leukocytosis, then among relatives of leukemic patients one should discover numerous elevated leukocyte counts. Videbaek felt that none of the reports to date could be accepted as indicative of familial latent leukemia but added no new data of his own. It would indeed be important if carriers of "leukemia genes" could be detected in a manner similar to that of the detection of apparently normal carriers of the low penetrance dominant gene involved in epilepsy (by electroencephalography) or of the recessive gene in hereditary leptocytosis (by blood examination). In the family here investigated, other relatives of the leukemic patients were studied with respect to the appearance of their peripheral blood, with an aim to detecting, if

9. Gross, L., and Matte, M. L.: The Occurrence of Tumors and Leukemia in Members of Families of Patients Suffering from Leukemia, New York State J. Med. **48**:1283-1284, 1948.

10. Busk, T.: Some Observations on Heredity in Breast Cancer and Leukemia, Ann. Eugenics **14**:213-229, 1948.

11. Gorer, P. A., in a review of Videbaek,[1] Ann. Eugenics **14**:346-348, 1949.

possible, any latent disorder. As tabulated earlier, these studies revealed no definite abnormality. However, in the cases of sibling 8, who later had the disease, and sibling 2, who displayed a leukemoid reaction before dying of pulmonary disease, the hematologist in retrospect felt that certain typical (for this family) early changes were present in the blood thrombocytes. To me it seems unique that a "normal" person was considered as potentially leukemic on genetic grounds alone, and that, although clinical studies failed to reveal evidence of leukemia, within a year the patient was dead of the disease. Before the child became ill, the family inquired about the likelihood of this boy and his siblings having the disease. This could not be answered except in very general terms. At present, however, it seems that the two surviving children have passed the critical age (for this family) and that their chances for acquiring the disease are small.

With respect to the health of more distant relatives, it should be mentioned that no other blood disorders, and only one case of cancer, occurred among the 135 recorded members of the pedigree (including 23 first cousins of the affected siblings). This information is known only by history and thereby loses some of its significance.

In view of the unusual blood findings presented by this family, a follow-up report will be made later by other authors in which hematological features will be described in detail.

SUMMARY AND CONCLUSIONS

A family is reported on in which five of eight siblings have had leukemia in early childhood. Except for a leukemoid reaction in another sibling, no other blood disorders, and only one case of cancer, are known among the 135 near and distant relatives.

A brief review is made of the literature dealing with hereditary factors in leukemia. It appears that a genetic factor is often involved, but it is premature to draw definite conclusions regarding the mode of inheritance. Workers generally favor the idea of a low penetrance dominant gene, but such a family as the one reported on in this paper would suggest instead a rare recessive gene with high penetrance. It may well be that in leukemia, as in many other diseases, the mode of inheritance varies in different families, owing to differences in the predisposing genes themselves.

Drs. Robert Hebel and Frances Schaar assisted in interpretation of the blood smears of nonaffected relatives. Dr. Irvine McQuarrie brought this unique family to my attention.

ADRENAL CORTEX EXTRACT IN PEDIATRICS

Possible Effect on the Respiratory System of the Newborn

R. WILLIAM PROVENZANO, M.D.
PHILIP McGOVERN, M.D.
R. SCHULTZ, M.D.
AND
JAMES HESTER, M.D.
BOSTON

THORN [1] considers and classifies acute adrenal insufficiency into three types. A fourth type of acute adrenal insufficiency, with congenital hypoplasia of adrenocortical tissue, occurs in the newborn infant.[2] The respiratory signs presented by a patient with this condition were definite. There was a disappearance of moist rales, cyanosis and dyspnea after replacement therapy. Because these manifestations recurred and increased in severity with the continued withdrawal of treatment with adrenal cortex extract, it appeared that adrenocortical hormone might exert a selective action on the cardiorespiratory system. This became more probable when a review of the records of several patients who suffered from a deficiency of this hormone revealed clinical and postmortem findings of pulmonary disease.[3] In addition, evidence has been presented that fatal hyalin-like membranes in the newborn might be caused by some injury to the epithelium and walls of terminal

---

From the Pediatric and Obstetrical Services, Cambridge City Hospital, Cambridge, Mass., and St. Elizabeth's Hospital, Brighton, Mass.

Pathologist in Chief, Cambridge City Hospital; Instructor of Pathology, Harvard Medical School, Boston (Dr. Schultz). Visiting Obstetrician and Gynecologist, Cambridge City Hospital, Boston City Hospital and St. Elizabeth's Hospital (Dr. Hester). Visiting Obstetrician and Gynecologist, Cambridge City Hospital, and St. Elizabeth's Hospital; Instructor in Obstetrics, Tufts Medical School (Dr. McGovern). Visiting Pediatrician, Cambridge City Hospital and Sancta Maria Hospital, Cambridge, Mass., and St. Elizabeth's Hospital; Pediatrician in Chief and Consultant in Pediatrics, Longwood Hospital, Boston, and Harley Hospital, Dorchester, Mass. (Dr. Provenzano).

The extract used in this study was supplied by The Upjohn Company, Kalamazoo, Mich., through the courtesy of H. F. Hailman, M.D., Ph.D., Medical Division.

1. Thorn, G. W.: Diagnosis and Treatment of Adrenal Insufficiency, Springfield, Ill., Charles C Thomas, Publisher, 1949.

2. Provenzano, R. W.: Adrenocortical Hypoplasia in the Newborn Infant, New England J. Med. **242**:87-89, 1950.

3. Thorn.[1] Provenzano.[2] Zuelzer, W. W., and Blum, A., Jr.: Adrenocortical Insufficiency in Infants with Adreno-Genital Syndrome, J. Pediat. **35**:344-361, 1949. Miller, R. A.: Shock in Newborn Infant, Arch. Dis. Childhood **16**:230-242, 1941. Conference at the New York Hospital-Cornell Medical Center, Jan. 14, 1949: Case II. Congenital Adrenocortical Insufficiency with Virilism, J. Pediat. **34**:768-777, 1949.

air spaces in pulmonary fields.[4] We believe that the nature of this injury is possibly explained by a condition resulting from a deficiency of this hormone.

It is the purpose of this paper to present both clinical and roentgenographic observations resulting from a study attempting to determine the possible action of adrenocortical hormone on pulmonary function in the newborn.

MATERIAL AND METHOD

The patients in this study were selected from private and clinic sources. The majority were delivered by one of us (P. M.), and obstetricians who delivered the others followed the same procedures, including induction of maternal anesthesia and analgesia. Alternate infants admitted to the nursery were given adrenal cortex extract.[5] An equivalent number served as controls. A twin in this study was treated as an individual birth. A roentgenogram of the chest was made of all patients in group 1 (40) at birth, and this procedure was repeated in 12 and in 24 hours. At these times, one of us (R. W. P.) observed the clinical progress with particular attention to the lung fields to establish the possible correlation of clinical and roentgenographic findings. All these patients were given divided hypodermic doses of 300 mg. of ascorbic acid and 10 mg. of a vitamin K analog. Those receiving the extract were given 2 cc. at birth. This dose was repeated within two hours and again in four hours.

Identical clinical studies were conducted on group 2, composed of infants (118) who had been given the hormone but had not had roentgenograms taken. The same number (118) served as controls. This group was observed to determine the clinical progress and the comparative incidence of respiratory difficulty. The results are summarized in relation to functions, such as activity, sucking reflex, respiratory signs and apparent muscular tone.

While this study was in progress, a group of 72 patients (group 3) with anoxemia and atelectasis was given the hormone extract as described. The results for these patients are summarized. Although the last group of patients served as a clinical, but not a controlled research, study group, the response obtained warrants the recording of the results and emphasizes the possible importance of the use of the drug in such patients. For some of these patients it was necessary to continue injections at 12 hour intervals for two to four doses. Rarely was a combined total dose of more than 12 cc. indicated in any one case.

RESULTS

Group 1, the patients who had roentgenograms taken, revealed on clinical examination moist inspiratory and expiratory rales at birth. These persisted after adequate aspiration of nasal and postpharyngeal areas. Twelve hours after birth 14 of the control series had rales on auscultation, as compared with five of the patients who were given adrenal cortex extract. Thus, six of the control and 15 of the experimental series revealed clear lung fields on auscultation at the end of 12 hours. After 24 hours one patient who received the extract continued to show rales, whereas eight of the control series revealed evidence of alveolar moisture. The roentgenographic findings did not confirm the clinical observations. Because of the technical difficulties in obtaining roentgenograms in the same respiratory phase, an exact statistical comparison is impossible. It is believed that rapid, serial films might aid in determining the nature of progression of pulmonary aeration with the use of the hormone extract. However, it is of interest to note that manifestations of respiratory distress were present in four patients, with only

4. Miller, H. C., and Jennison, M. H.: Study of Pulmonary Hyaline-like Material: 4,117 Consecutive Births, Pediatrics **5**:7-20, 1950.

5. Adrenal cortex extract, a biologically standardized extract, is prepared from adrenal glands containing the cortical activity that is essential for life. Each cubic centimeter contains not less than 50 dog units or 2.5 rat units.

one showing evidence of atelectasis. Of the patients who had clear lung fields on roentgenograms and who did not receive the extract, respiratory distress developed in one within 12 hours. Three of the patients with normal respiration at birth, who presented evidence of atelectasis on roentgenograms, later manifested respiratory distress. These three patients did not receive the hormone extract.

In the second group 236 patients were studied. One hundred and eighteen received the adrenal cortex extract, and the same number served as controls. At

TABLE 1.—*Comparison of Results on Auscultation in Controls and in Infants Given Adrenal Cortex Extract (Group 1)*

		Control Series	Series Given Adrenal Cortex Extract
At birth	Rales	20	20
	Clear	0	0
12 hr. after birth	Rales	14	5
	Clear	6	15
24 hr. after birth	Rales	8	1
	Clear	12	19

TABLE 2.—*Comparison of Results in Control Series and in Series Given Adrenal Cortex Extract (Group 2)*

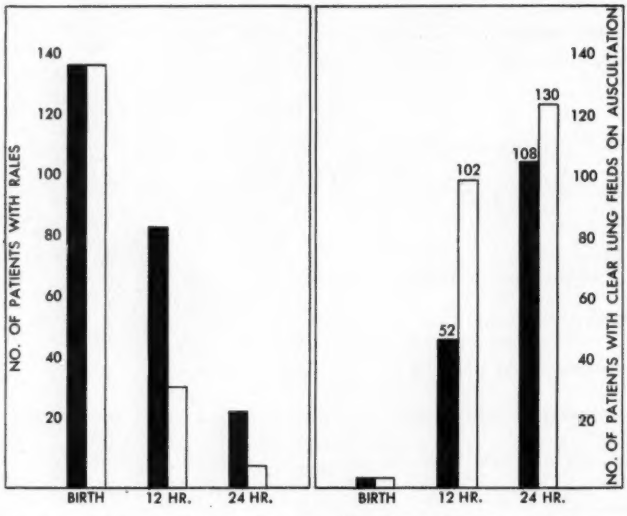
Auscultation		Control Series	Series Given Adrenal Cortex Extract
At birth	Rales	118	118
	Clear	0	0
	Dyspnea	16	12
12 hr. after birth	Rales	72	31
	Clear	46	87
	Dyspnea	7	2
Pulmonary fields, 24 hr. after birth	Rales	22	7
	Clear	96	111
	Dyspnea	3	0
Sucking reflex, 12 to 24 hr. after birth	Good	29	77
	Fair	56	24
	Poor	33	17
Muscular tone and activity, 24 hr. after birth	Good	37	82
	Fair	53	20
	Poor	28	16
Complications			
1. Atelectasis		4	1
2. Death		2 (Heart disease and atelectasis)	1 (Heart disease)

birth moist inspiratory and expiratory rales were heard in all patients of both series. Prolonged and difficult grunting and retracting respirations occurred in 24 patients. Of these 24 patients who presented respiratory distress, eight received adrenal cortex extract, and the remainder were in the control series. Those given the extract showed more rapid clearing of symptoms, with all but two having clearing within eight hours. Some patients not receiving the hormone extract continued to show mild to moderate distress after eight hours, and seven of these 16 patients showed no clearing of manifestations after 12 hours.

Twelve hours after birth 31 of the infants given hormone treatment revealed rales, as compared with 72 in the control series. Thus, 87 who received the extract showed clearing of lung fields on auscultation, as compared with 46 infants

in the control series. Two patients who received the extract continued to have difficult respiration which cleared within 12 to 14 hours. Seven newborn infants not receiving the hormone extract showed evidence of difficult respiration after 12 hours, and in three of these manifestations continued after 24 hours. (The figure summarizes auscultatory findings for groups 1 and 2.)

It is difficult to judge comparatively and conclusively on statistical bases the effects of medication on the newborn infant, especially in relation to sucking reflex, apparent muscular tone and activity. A general comparison can, nevertheless, be made. In general, it was noted that the sucking reflex was stronger, the muscular tone better maintained and the activity and color of the newborn infant more satisfactory in the treated series when compared with that in the series not receiving the adrenal cortex extracts. Twenty-four hours after birth 77 patients



Summary of auscultatory findings in 138 controlled patients (groups 1 and 2). Solid columns indicate numbers of controls; white columns, the numbers receiving adrenal cortex hormone.

receiving the extract showed a good, 24 a fair, and 17, a poor, sucking reflex. On the other hand, of those not receiving the extract, only 29 were considered to have a good sucking reflex; 56 had a fair, and 33 patients, a poor, sucking reflex.

A consideration of muscular tone and activity followed a similar outline. There were 82 treated infants who revealed good muscular tone and good activity, as compared with 20 patients with fair and 16 patients with poor muscular tonicity and activity, whereas in the control series 37 had results that were classified as good, 53 as fair and 28 as poor. Vomiting occurred in both series, but vomiting occurring for the first time 24 hours after birth was reported in 19 patients not receiving hormone extract and in five patients in the experimental series. Projectile vomiting was reported in 14 patients of the control series and in three patients receiving the extract.

In this group the clinical diagnosis of symptomatic atelectasis was confirmed for five patients, This included one patient who received the extract and four patients who did not. On the administration of the extract, in the one patient symptomatic improvement occurred more rapidly than in the infants of the control series. There were three deaths in this group, and the causes of death were found to be congenital heart disease and atelectasis.

In group 3, adrenal cortex extract was given to anoxic patients. It is in this group of patients in which the "stress and strain" component becomes manifest that the more startling therapeutic responses seemed to have occurred. The signs, symptoms and complications of anoxia have been discussed by Clifford [6] and others.[7] The causes for the anoxemia in this group are listed (table 3). Be it sufficient to state that the diagnosis of anoxemia was based on the presence of all or several of the following signs: persistent or intermittent cyanosis; irregular or apneic respirations, with the majority of patients showing dyspnea with sternal retraction

TABLE 3.—*Causes of Anoxemia in Group 3*

	Number of Patients	Number with Atelectasis
Prematurity	24	9
Erythroblastosis fetalis	8	3
Cesarean section	7	4
Premature separation	5	1
Prolapsed cord	2	..
Cerebral injury	5	1
Pneumothorax	2	2
Infection (aspiration)	7	6
Anesthetization	2	..
Medication	2	..
Congenital heart disease	3	..
Toxemia	5	1
Total	72	27

and grunting respirations; and usually weak and often cephalic cry. Irrespective of the cause of anoxemia, the patients were given adrenal cortex extract immediately, along with ascorbic acid, vitamin K analogs and general supportive treatment.

Of the 72 patients, 27 showed evidence of atelectasis (table 3). The patients who responded to therapy manifested signs of improvement within eight to 24 hours. The response was at times remarkable, and it seemed to be in relation to time of administration of the drug and onset of disease manifestations. The sooner the hormone was given, the more effective its use appeared to be. Clinical improvement with general muscular and respiratory activity was noted. Cyanosis diminished, the cry became less feeble and moisture in lung fields was clinically largely absorbed. Oxygen therapy was no longer necessary, sufficient pulmonary function being restored with no dyspnea, grunting or retraction. In this group

6. Clifford, S. H.: Fetal Anoxia at Birth and Cyanosis of the Newborn, Am. J. Dis. Child. **76**:666-678 (Dec.) 1948; Management of Emergencies, ibid. **73**:706-712 (June) 1947; Care of Newborn, New England J. Med. **240**:61-67, 1949.

7. Flagg, P. T.: Treatment of Postnatal Asphyxia, Am. J. Obst. & Gynec. **21**:537-541, 1931. Smith, C. A.: Round Table Discussion on Neonatal Asphyxia, J. Pediat. **19**:258-273, 1941.

there were seven deaths. Two were due to congenital heart disease, one to cerebral damage, one to atelectasis and three to prematurity. Three patients showed evidence of sequelae of anoxia. The remainder of patients in this group were normal in all respects. Fifty-one patients followed since birth have shown no ill effects from the use of the extract. The growth and development of these patients have been satisfactory after three years.

COMMENT

The results of the administration of adrenal cortex extract in these newborn infants suggests the use of this drug in effecting the more rapid clearing of the respiratory system. This may prevent epithelial damage to alveolar membranous structures. The mechanism whereby this is accomplished is not exactly known. It might be a direct effect through the hormonal group action of the extract or an effect secondary to the improvement in the vascular and muscular tonicity of the infant, whereby material present in the lung field at birth is more rapidly absorbed.

The beneficial effects noted in response to treatment of anoxia in the newborn justify the administration of the extract for this condition. To allow more critical evaluation of the effect on the newborn, further investigation is necessary, but administration of adrenal cortex extract to the patients described has not produced any complications contraindicating its use.

SUMMARY

The clinical effect of adrenal cortex extract on the respiratory system of newborn infants is noted. The effect of this hormone on activity, sucking reflex, muscular tone and respiratory manifestations of newborn infants is summarized. The beneficial results of the extract in treatment of patients with anoxemia are mentioned. It is hoped that other investigators will evaluate the use of this substance for newborn infants showing ill effects from anoxia, irrespective of cause, in order that the true value of adrenal cortex extract be established.

C. De Foe, R.N., and Sister St. Claire, R. N., assisted in the preparation of statistical materials. William Carey, M.D., roentgenologist at St. Elizabeth's Hospital, and Edward Leary, M.D., of Cambridge City Hospital, assisted in interpretation of roentgenograms.

PREVENTION OF MINOR SKIN IRRITATION (MILIARIA) AND IMPETIGO IN THE NEWBORN

JEROME GLASER, M.D.
ROCHESTER, N. Y.
MARVIN L. THOMPSON, M.D.
BERLIN, N. Y.
AND
THOMAS D. BENSON, M.D.
ROCHESTER, N. Y.

THE PURPOSE of this paper is to assess the value of a new antiseptic compound hexachlorophene, in preventing infection of the skin of newborn infants.

The occurrence of impetigo and various minor skin irritations, grouped, for want of a better name, under the term "miliaria," is a perennial problem in almost every obstetric and pediatric service. Not only does superficial infection of the skin constitute a potential danger to the patient, but the new mother is particularly disturbed both mentally and physically when she learns that her infant has an "infection" which in many instances prevents her seeing the baby for several days.

Sanford [1] has recommended that the infant be given no bath or other skin treatment for the first nine days of life. However, the fact that pustular eruptions are too frequent occurrences during infancy raises a question as to the advisability of this plan. Chadwell,[2] in 1928, urged the use of ammoniated mercury ointment, but to us the evidence was not convincing that this would be the procedure of choice.

Since 1943 the routine technic for the care of the skin of newborn infants in the nursery of the Genesee Hospital had been the use of 5 per cent sulfathiazole cream. Each infant after a soap and water bath was given a single inunction with this cream. Soap and water bathing and the use of liquid petrolatum for cleansing the diaper area were the only other procedures used for the rest of the hospital stay. With the use of this technic skin infection dropped to a minimum. An average of two cases of impetigo a year occurred during the following three years. No cases of sensitivity of the skin to sulfathiazole were noted.

Despite the favorable results of this procedure, we sought for some other agent to use for two reasons: (1) to give mothers an effective preparation that could be used at home for continued skin care without danger and (2) because use of

This study was made possible by a Grant-In-Aid from Johnson & Johnson, New Brunswick, N. J.

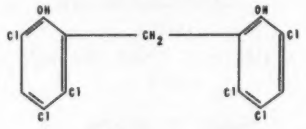
From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry and the Pediatric Service of the Genesee Hospital.

1. Sanford, H. N.: Care of Skin of Newborn Infant: 6-Year Study of 3,500 Newborn Infants, J. Pediat. **11**:68 (July) 1937.

2. Chadwell, O. R.: Impetigo Neonatorum: Its Control and Treatment, New England J. Med. **199**:983 (Nov. 15) 1928.

sulfathiazole has produced an unusually high incidence of sensitivity and has been dropped from the "New and Nonofficial Remedies" by the Council of Pharmacy and Chemistry of the American Medical Association.[3]

Our attention was called [4] to a compound [5] having strong antibacterial properties, for which the generic term "hexachlorophene" was adopted by the Council on Pharmacy and Chemistry of the American Medical Association.[6] The chemical designation of this compound [7] is 2,2′-dihydroxy-3,5,6-3′,5′,6′-hexachlorodiphenyl methane. The following is its structural formula:



This substance is a halogenated dihydroxydiphenyl methane which, as the name implies, is a homolog and analog of phenol and its halogenated derivatives; in the early literature it was referred to as "G-11."

Hexachlorophene appears to be a highly satisfactory antiseptic; an unusual property is its prolonged duration of action. It is a colorless solid with a melting point of 164 C.; it is practically odorless; poorly soluble in water, but readily soluble in ketones, and slightly soluble in mineral oils and hydrocarbon solvents, but soluble in many of the fatty acids and their esters. Alkali salts are readily prepared. Phenol coefficient determinations made according to the standard Food and Drug Administration procedure showed that this product has a Staphylococcus aureus coefficient of 125 ± 25 at 37 C. and 111 ± 25 at 20 C. The Salmonella typhosa coefficient is about 20 at each temperature. Its antibacterial properties are well maintained in watery solutions and in the presence of soaps, but when dissolved in substances such as liquid petrolatum its activity is decidedly limited.[8]

Traub, Newhall and Fuller,[9] impressed by the potential value of this substance, studied its effect on the bacterial flora of the human skin when incorporated into

3. Sulfonamides for Local Application Deleted from N. N. R., Council on Pharmacy and Chemistry, J. A. M. A. **135**:157 (Sept. 20) 1947. Danger from External Use of Sulfonamides, Council on Pharmacy and Chemistry, ibid. **128**:1024 (Aug. 4) 1945. Lyons, C.: Chemotherapy in the Management of Wounds, ibid. **133**:215 (Jan. 25) 1947. Resolutions on Use of Sulfonamides, Minutes of Annual Session of the American Medical Association, Chicago, Dec. 3-5, 1945, ibid. **129**:1194 (Dec. 22) 1945. Annual Meeting of the Council on Pharmacy and Chemistry, ibid. **136**:691 (March 6) 1948.

4. By Dr. John Henderson, Medical Director of Johnson & Johnson.

5. Cade, A. R.: New Disinfectants, Soap & San. Chem. **20**:111 (Feb.) 1944; Givaudanian, April 1944, p. 1.

6. Hexachlorophene, Generic Term for bis (2-hydroxy-3,5,6-trichlorophenyl) methane, Council on Pharmacy and Chemistry, J. A. M. A. **136**:471 (Feb. 14) 1948.

7. Hexachlorophene is manufactured by Sindar Corporation, New York 18.

8. Henderson, J.: Personal communication to the authors.

9. Traub, E. F.; Newhall, C. A., and Fuller, J. R.: The Value of a New Compound Used in Soap to Reduce the Bacterial Flora of the Human Skin, Surg., Gynec. & Obst. **79**:205 (Aug.) 1944; New Cutaneous Bactericidal Agent Used in Soap, Arch. Dermat. & Syph. **52**:385 (Nov.-Dec.) 1945

a soap, using a modification of the Price scrubbing technic.[10] They found that 2 per cent hexachlorophene thus employed enabled the subjects to maintain an exceedingly low bacterial population on the skin of the hands and forearms and demonstrated that a persistent reduction in the resident bacteria of the human skin occurs when the soap is used routinely. Furthermore, hexachlorophene was shown to be active against pathogenic as well as nonpathogenic bacteria. There was no irritation of the skin, as judged by more than 200 patch tests. These were repeated on the same subjects after 10 to 14 days and again were found to give negative results, thus showing that sensitivity of the skin had not been produced by the first test. Subjects using soap containing hexachlorophene regularly for one year showed no evidence of irritation.

Hexachlorophene has been found highly active in reducing and suppressing the bacterial flora of the skin when in soap regularly used as a surgical scrub.[11] This action is persistent for some period after use of the soap is discontinued.

It was obvious, in the light of these considerations, that the use of hexachlorophene in a suitable base for the care of the skin of the newborn merited careful study. Its continued use on the infant's skin by the mother after leaving the hospital might be feasible and possess no potential dangers. It seemed probable that a lotion type vehicle, consisting of an oil-in-water emulsion, would prove to be the most satisfactory for our purposes because when dissolved in oil the activity of hexachlorophene is reduced.

Two types of lotion containing the compound hexachlorophene were supplied to us for study through the courtesy of the Department of Clinical Research of Johnson & Johnson. These consisted of emulsions of liquid petrolatum and hydrous wool fat in water to which hexachlorophene had been added (except in the control preparation), the one slightly acidic, the other slightly basic. A concentration of 1 per cent hexachlorophene was arbitrarily chosen as roughly corresponding to the 2 per cent concentration which had proved effective in the case of the liquid soap on which the original experimental observations had been based. Each lotion was given a code number and was subjected to a clinical trial without our knowing at the time the composition of the material employed. The infants in the newborn nursery were divided into three approximately equal groups. One group served as a control in which the sulfathiazole routine described above was continued unmodified. The following is the technic used for the experimental groups.

As soon after birth as a normal rectal temperature was obtained, the infant was given a soap and water bath followed by an inunction with the lotion containing hexachlorophene.

10. Price, P. B.: The Bacteriology of Normal Skin; A New Quantitative Test Applied to Study of Bacterial Flora and Disinfectant Action of Mechanical Cleansing, J. Infect. Dis. **63**:301, (Nov.-Dec.) 1938; New Studies in Surgical Bacteriology and Surgical Technique, with Special Reference to Disinfection of Skin, J. A. M. A. **11**:1993 (Nov. 26) 1938; Mercuric Chloride, Potassium Mercuric Iodide and Harrington's Solution in Skin Disinfection: Behavior and Uses, Surg., Gynec. & Obst. **69**:594 (Nov.) 1939.

11. Clark, D. G. C.; Lockwood, J. S., and Lewit, E.: 2,2'-dihydroxy-3,5,6-3',5',6' hexachlorodiphenylmethane (G-11) as an Antiseptic for Use in Surgical Scrubbing, Surgery **22**:360 (Aug.) 1947. Seastone, C. V.: Observations on the Use of G-11 in the Surgical Scrub, Surg., Gynec. & Obst. **84**:355 (Aug.) 1947. Fahlberg, W. J.; Swan, J. C., and Seastone, C. V.: Studies on the Retention of Hexachlorophene (G-11) in Human Skin, J. Bact. **56**:323 (Sept.) 1948. Seastone, C. V., and Erickson, T. C.: A Comparison of Solid and Liquid Soap as Vehicles for G-11 (Hexachlorophene) in the Surgical Wash, Surgery **25**:290 (Feb.) 1949. Nungester, W. J.; Thirlby, R. L., and Vial, A. B.: Evaluation of Hexachlorophene and Detergents as Substitutes for the Surgical Scrub: A Biological Technique, Surg., Gynec. & Obst. **88**:639 (May) 1949. Traub, Newhall and Fuller.[9]

The general inunction consisted in the following steps: 1. From an individual bottle the nurse poured a small amount of the substance to be investigated into her palm and applied it to the baby's face, scalp, ears (front and back) and neck. 2. The lotion was applied to the chest, axillas, arms, hands and abdomen. 3. The baby was turned and the lotion applied to the back. 4. The baby was turned and the lotion applied to the feet.

The infant received a daily soap and water bath. Each time a diaper was changed, the anus and buttocks were cleansed with the lotion in order to remove gross contamination and leave a discontinuous protective film of liquid petrolatum and hydrous wool fat as a prophylactic measure against diaper rash.

This program was carried out in the two newborn nurseries of the obstetric service during a 12 month period in which the number of deliveries reached a new high for the service because of the postwar period. Because the nurseries were overfilled at all times, there was a high potential danger of skin and other infections.

In addition to our observations with respect to the prevention of impetigo, we were interested in determining what the incidence of miliaria (prickly heat or sudamina) would be during this study, since it is the most frequent skin disease of the newborn infant.

According to MacKee and Cipollaro,[12] the eruption of miliaria consists of a multitude of discrete but closely set pinhead-sized red papules and vesicopapules, with some erythema surrounding the individual lesions. The eruption usually disappears within a few days to two weeks, at which time slight desquamation is frequent. Impetigo, intertrigo, boils, small abscesses and pustules are common complications. In adults subjective symptoms are mild pruritus and a stinging sensation.

RESULTS

Experimental lotion 228-D was used on only 10 patients; in two of these impetigo developed. Because of its obvious lack of effectiveness in preventing this condition, the use of this lotion was discontinued without further study. Since this preparation was intended as a control, it contained only the vehicle (liquid petrolatum, hydrous wool fat and water) without the addition of the hexachlorophene or other antiseptic agent.

Lotion 253 was used on 356 infants. This was similar to the control material 228-D, with the addition of hexachlorophene in a concentration of 1 per cent; the p_H of this preparation was adjusted, by means of a suitable buffering system, to approximately 5.5. In this series 10 cases of miliaria rubra occurred; in one infant a marked irritation of the buttocks developed but cleared when use of the lotion was stopped, and in one infant a very mild impetigo developed on the day of discharge, the sixth day of life.

Lotion 246[13] was used on 692 infants. This was similar to lotion 253 except that the buffer system was adjusted for a p_H of 8.45 so that the preparation had a slightly alkaline reaction. In this series 10 cases of miliaria rubra developed, of which three were considered severe but were not thought to be directly attributable to the use of this lotion. In one infant an isolated furuncle of the scalp developed.

There were 562 infants in the sulfathiazole-treated group. Among these there occurred six cases of miliaria rubra, two of which were severe, and in one infant a furuncle of the left elbow developed.

---

12. MacKee, G. M., and Cipollaro, A. C.: Skin Diseases in Children, ed. 2, New York, Paul B. Hoeber, Inc., 1946, p. 285.

13. This is available as Johnson's Baby Lotion with 1 per cent hexachlorophene.

The results of our observations are summarized in the table.

In interpreting these statistics, it should be realized that a general connotation is implied in the term miliaria, under which we have included all types of minor skin eruptions due to various types of irritation and minor nonspecific infection. Under this category are included many cases of so-called diaper rash, since no special study of this condition was made during this investigation, it merely being observed that the general incidence of diaper rash was considerably decreased when the hexachlorophene lotions were used. This is understandable in the light of the high degree of antibacterial activity of this preparation for Bacterium ammoniagenes, which has been shown by Cooke [14] and by Benson and co-workers [15] to be the most important causative agent of ammonia dermatitis. This condition is more frequently seen in the home than under hospital care and does not commonly occur during the newborn period.

COMMENT

From the standpoint of results, there is statistically little difference between the sulfathiazole and the hexachlorophene types of treatment on the basis of this limited series. We feel it fair, however, to conclude from this study that hexachlorophene-

Results of Observation of 1,610 Infants

		Miliaria		Infection	
	No. of Infants	No. of Cases	Per Cent	No. of Cases	Per Cent
Control	562	6	1.07	1	0.18
Lotion 253	356	10	2.08	1	0.28
Lotion 246	692	10	1.4	1	0.14
Total infants receiving experimental lotions	1,048	20	1.9	2	0.19

containing lotions, when used in the manner described, are at least as effective as sulfathiazole in the prevention of infections of the newborn and are superior in that their use is lacking in the hazards known to accompany the topical use of sulfathiazole. Furthermore, through the use of preparations of this type, there is minimal likelihood of sensitizing the skin of the infant in such a manner as to be a possible source of difficulty in later life.

In regard to the acid and alkaline types of lotion, each containing the same concentration of hexachlorophene, in spite of theoretical considerations which might lead one to believe that the acid lotion would prove superior, the mildly alkaline lotion (246) appeared to be somewhat better tolerated. Both types of lotion were highly effective in controlling the incidence of impetigo. The fact that the incidence of this condition was somewhat less with the alkaline-lotion-treated series is readily accounted for by the greater antibacterial activity of the alkaline complex in which hexachlorophene is present in this preparation.

14. Cooke, J. V.: The Etiology and Treatment of Ammonia Dermatitis of the Gluteal Region of Infants, Am. J. Dis. Child. **22**:481 (Nov.) 1921; Dermatitis of the Diaper Region in Infants (Jacquet Dermatitis), Arch. Dermat. & Syph. **14**:539 (Nov.) 1926; in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., vol. 4, chap. 41, 1936.

15. Benson, R. A.; Slobody, L. B.; Lillick, L.; Maffia, A., and Sullivan, N.: The Treatment of Ammonia Dermatitis with Diaparene: Report on 500 Cases, J. Pediat. **34**:49 (Jan.) 1949.

It should be noted that the infants of the control (sulfathiazole) group were kept in a nursery on the second floor which serves the mothers who have private rooms. This nursery is ideally situated for the prophylaxis of infections, being off the main thoroughfare. The nursery on the first floor serving the semiprivate and ward patients, however, is opposite the delivery room and near the main desk where the traffic is heavy at all times. The infants of the two groups receiving the lotions were kept in the latter nursery and therefore at least theoretically were subjected to a heavier exposure to infection than the sulfathiazole-treated group.

On discharge the routine skin care with lotion 246 was continued uninterruptedly by the mothers at home. In our private practice over the past two years not a single instance of contact dermatitis has been observed. Our findings in this regard have consistently been negative, in spite of the fact that a lotion containing hexachlorophene has been used many times a day on over 1,048 infants, some of whom have received this treatment uninterruptedly for as long as 18 months.

SUMMARY AND CONCLUSIONS

A technic employing sulfathiazole ointment, which was established to control an undue incidence of impetigo, is described. So far as could be determined, this proved satisfactory during the period of use, but is no longer recommended.

A similar technic with use of hexachlorophene in a concentration of 1 per cent in a bland oil-in-water lotion type base was found to be highly effective in controlling the incidence of impetigo and miliaria in newborn and older infants.

The sulfathiazole technic is open to the objection that it may cause sensitiveness to sulfonamide compounds in later life or lead to other undesirable sequelae. There is no objection of a similar nature in the case of hexachlorophene, and therefore the use of this substance is considered to be a highly satisfactory procedure.

An oil-in-water emulsion having a slightly alkaline p_H and containing hexachlorophene in a concentration of 1 per cent (lotion 246) was found to be somewhat superior to a similar lotion having a slightly acid p_H. The alkaline product was found to be unusually satisfactory in the routine care of the skin of infants beyond the newborn period and to be prophylactically effective in minimizing the incidence of diaper rash and miliaria.

Mrs. Kathleen Burrows, Nursery Supervisor of the Newborn Service of the Genesee Hospital, cooperated during the course of this study.

ADVERSE MERCURIAL REACTIONS IN THE FORM OF ACRODYNIA AND RELATED CONDITIONS

JOSEF WARKANY, M.D.
AND
DONALD M. HUBBARD, Ch.E.
CINCINNATI

ACRODYNIA is a symptom complex which is easily recognized in the fully developed form. According to Bilderback,[1] the outstanding symptoms are pink hands and feet, desquamation, scarlet cheeks and tip of nose, alopecia, salivation, loss of several or all of the teeth, occasional loss of nails or phalanges, excessive perspiration, evanescent rashes, marked hypotonia, itching, burning and severe pain of the extremities, increased pulse rate and blood pressure, photophobia, insomnia and apathy alternating with extreme irritability. If the manifestations of the disease are mild or are associated with complications, the diagnosis may be doubtful. None of the above symptoms is alone diagnostic for the disease, and opinions differ concerning the cardinal changes of acrodynia. Some authors consider the nervous manifestions of the disease essential for the diagnosis, while others emphasize cutaneous or cardiovascular symptoms. In spite of the diagnostic uncertainties the syndrome is well established as a disease entity.

Many theories exist concerning the causation of acrodynia.[2] It has been considered a postinfectious, infectious (viral), allergic, endocrine or toxic disorder; a deficiency disease; a neurosis of the vegetative nervous system, or a disease of the gastrointestinal tract. None of these theories found general recognition, and none of them led to effective preventive or therapeutic measures.

The concept of acrodynia as a toxic disorder has much in its favor. The nature of the symptoms, the absence of fever and the protracted course of the disease, which in the majority of cases ends in recovery, suggest an intoxication. Ergot,[3] Ustilago maydis [2c] and particularly arsenic were frequently investigated as possible causes of acrodynia. Chronic arsenic intoxication has many symptoms in common with acrodynia, such as muscular weakness, apathy, burning pain in the extremities,

From the Children's Hospital Research Foundation and the Department of Pediatrics and the Kettering Laboratory of Applied Physiology, University of Cincinnati.

1. Bilderback, J. B.: Acrodynia, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, vol. 4, chap. 20.

2. (*a*) Bilderback.[1] (*b*) Péhu, M., and Boucomont, J.: Sur l'acrodynie infantile: Relations et parentés pathologiques de l'acrodynie infantile, Rev. franç de pédiat. **12**:277, 1936. (*c*) Mayerhofer, E.: Die Akropathien des Kindesalters mit besonderer Berücksichtigung der infantilen Akrodynie, Ergebn. d. inn. Med. u. Kinderh. **54**:269, 1938. (*d*) Cheek, D. B.: Pink Disease: An Investigation of Its Cause and Treatment, M. J. Australia **1**:101 (Jan. 28) 1950. (*e*) Cheek, D. B., and Hicks, C. S.: Pink Disease or Infantile Acrodynia: Its Nature, Prevention and Cure, ibid. **1**:107 (Jan. 28) 1950.

3. Debré, R., and Nevot, A.: Sur le problème de l'étiologie de l'acrodynie infantile, Ann. pædiat. **152**:253, 1939.

anorexia, loss of weight, stomatitis, conjunctivitis, lacrimation, scarlatiniform rashes, redness of the hands and feet, desquamation and alopecia. However, in chronic arsenic poisoning gastrointestinal symptoms, permanent paralyses, dryness of the skin, melanosis and keratosis are characteristic changes which do not occur in infantile acrodynia. It is probable that the epidemic of acrodynia which occurred in France in 1829 was actually due to arsenic poisoning, as suggested by Petrén [4] and Péhu and Ardisson [5]; but there is general consensus that this epidemic, which chiefly affected adults, was not identical with the infantile acrodynia observed in the twentieth century. In two of the first cases of acrodynia described in children in this country, Byfield [6] considered arsenic poisoning as a possible cause; but he was unable to find arsenic in the urine. In 1922 Davis [7] investigated the possibility of arsenic poisoning in a child with acrodynia but could neither discover a source of intoxication nor demonstrate excretion of arsenic in the urine. However, in 1933 arsenic and lead were found in appreciable amounts in the blood and urine of a patient with acrodynia reported on by Meyer and Weise.[8] The authors thought that arsenite of lead, which is used as a parasiticide, was the source of the metals in their case. Calvin and Taylor [9] reported significant amounts of arsenic in the hair and in the urine of a patient with acrodynia, and lead was detected in the blood 12 weeks after admission. The authors suggested that acrodynia is "arseno-plumbism" in peculiarly susceptible persons. Ecker [10] observed significant amounts of arsenic in the brain in one of two persons with acrodynia examined. Most of the investigators who reported cases of acrodynia could not find proof of arsenic poisoning and rejected the theory of arsenism in this disease.

We also had always been impressed by the similarity of many symptoms of chronic arsenic poisoning to those of acrodynia. On several occasions we submitted blood and urine samples from children with acrodynia to the Kettering Laboratory in the College of Medicine of the University of Cincinnati to be tested for arsenic, but excessive amounts were never found. In April 1945, another patient with typical acrodynia was admitted to the Children's Hospital of Cincinnati and blood and urine specimens were again submitted to the Kettering Laboratory. On this occasion we asked more generally for "qualitative metal determinations," hoping that a metal other than arsenic might be discovered. A detailed report of this case follows.

CASE 1.—M. C., a girl 14 months old, was admitted to the Children's Hospital on April 20, 1945 because of a rash and irritability. She had been well until 10 weeks before admission. At that time many teeth erupted. Her gums were swollen, and she became irritable and cried

4. Petrén, K.: L'acrodynie: Une intoxication arsénicale, Rev. neurol. **28**:812, 1921.

5. Péhu, M., and Ardisson, P.: Une maladie qui ressuscite: L'acrodynie, Paris méd. **1**: 341, 1927.

6. Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children, Am. J. Dis. Child. **20**:347 (Nov.) 1920.

7. Davis, C. M.: Acrodynia (?), Arch. Pediat. **39**:611, 1922.

8. Meyer, F., and Weise, E. C.: Acrodynia: Arsenic as the Etiologic Factor, J. Pediat. **2**:750, 1933.

9. Calvin, C. V., and Taylor, C. C.: Acrodynia: Its Possible Cause, J. Pediat. **6**:385, 1935.

10. Ecker, A. D.: Arsenical Content of the Brain in Cases of Encephalitis, Inflammatory Occlusion of Aqueduct, and Acrodynia, Proc. Staff Meet., Mayo Clin. **14**:43, 1939.

a great deal. She had no fever but lost 7 to 8 pounds (3,175 to 3,629 Gm.), although she ate fairly well. Three days before admission to the hospital a rash appeared on her back, abdomen and shoulders. She perspired profusely, but there was no reddening of the palms and soles, conjunctivitis or photophobia. At the time of the appearance of the rash the child became constipated and did not void for 36 hours. On the day following admission the child was irritable and listless; she was relaxed, lay with legs drawn up, perspired and had a rash characteristic of sudaminal eruption. She did not rub her hands but held them. She had a pulse rate of 180 when quiet. The blood pressure taken while she was quiet was 130/90. The child had no photophobia. The findings agreed very well with those in acrodynia.

Results of routine urine examination were normal except for a 1 + reaction for albumin on April 20. On the same day a hemoglobin value of 13.2 Gm. was recorded. The white blood cell count was 11,200. The differential count showed 72 per cent polymorphonuclear leukocytes, 24 per cent lymphocytes and 4 per cent monocytes.

On April 24 the child's picture had changed little, but she began to rub her hands together or put them in her mouth, which was sore. Perspiration was profuse. She showed miliaria, and the hands were wet and clammy. Two spinal fluid examinations were done, one on April 23 and one on May 7, and normal findings were obtained. The Wassermann reaction was negative.

On April 26 a blood sample and a urine sample were sent to the Kettering Laboratory for "qualitative metal determinations." The blood contained 0.035 mg. of lead per 100 Gm. This value is within normal limits. The blood was analyzed spectrographically, and lead, tin, aluminum, copper, manganese and silver concentrations were found to be normal. Antimony, cadmium, cobalt and thallium were absent. In the urine lead, tin, aluminum, copper, manganese, silver, arsenic, antimony, cobalt, thallium and cadmium were absent. At the suggestion of Mr. Jacob Cholak a quantitative mercury determination was made on the urine, and 360 micrograms of mercury per liter was found by the method of Hubbard. Since this is a high value, another urine specimen was submitted for determination on May 7, and again 320 micrograms of mercury per liter was found.

The child remained in the hospital three weeks. During this time she had frequent elevations of temperature; it was difficult to feed her properly, and she remained irritable and negativistic throughout her stay in the hospital. The pulse rate was 130, and blood pressure readings were 180/100, 160/76 and 115/70. The child was taken home on May 11, returning to the outpatient clinic on May 23. Her weight was 17 pounds (7,711 Gm.), but her appetite had improved. She was less irritable at home; her skin was moist, and the rash was still evident on the trunk and extremities. The gums were red, but the mother stated that her mouth appeared less sore. She had no photophobia.

Little change could be noticed in the child's condition when she returned to the outpatient clinic on May 31, 1945. On June 20 the stomatitis was definitely improved, and her disposition was better. She began to sit up. The weight was 17 pounds 5 ounces (7,853 Gm.), but she did not eat well. The rash persisted, and distinct swelling of the lymph nodes in the inguinal regions was noted. The child was not reexamined until July 30, 1948, when one of us visited the family in their home and found the patient well and healthy. On this occasion the mother said that the child had been given "cold tablets" before she became ill.

The source of the mercury found in the urine of this child could not be ascertained. However, the finding of a heavy metal in the urine of a child with acrodynia was of sufficient interest to lead us to pursue the study, and we planned to examine for mercury urine from children with acrodynia, as well as from persons who did not have the disease. Acrodynia is rare in Cincinnati, and only a few children with this disease have been seen in this hospital in recent years. However, after discussing our findings with pediatricians from other cities, we have been able to obtain additional urine specimens and case histories of children with acrodynia observed by them. These case reports are briefly recorded in this paper.

METHOD OF MERCURY DETERMINATION IN THE URINE

The method used for the determination of mercury in urine has been described by Hubbard.[11] Urine samples to be analyzed should be collected in pyrex® glass containers, previously washed with hot dilute 50 per cent (V/V) nitric acid (C. P. reagent), followed by rinsing with distilled water, to remove any trace of surface contamination. The size of each sample should be at least 50 ml. A lesser amount may be used whenever it is impossible to obtain 50 ml., although this amount is preferable for maximum accuracy of determination, especially when the mercury present in the samples is less than 1 microgram. The urine sample is digested in the presence of sulfuric acid and potassium permanganate by boiling under reflux until the permanganate color persists. After cooling the excess permanganate is reduced to a clear solution by the addition of hydroxylamine hydrochloride, and the mercury is extracted as a red organic complex with a solution of dibetanaphthylthiocarbazone in chloroform. After separation the chloroform layer is shaken with thiosulfuric acid whereby another mercury complex is formed in the aqueous phase, while copper, the only interfering element, remains in the chloroform. In order to break up the newly formed mercury complex the aqueous phase is treated again with acid potassium permanganate, and subsequently the excess permanganate is removed with hydroxylamine hydrochloride. This acid solution, containing the mercury in ionizable form, is cooled, and the mercury is extracted for the final analysis by the addition of a chloroform solution of dibetanaphthylthiocarbazone. The concentration of the latter reagent is chosen according to the two ranges to be used, namely, 0 to 5 micrograms or 0 to 50 micrograms of mercury. The accuracy for the former range is ± 0.2 microgram and for the latter range ± 0.5 microgram.

Density readings are made with a Beckman photoelectric spectrophotometer, but any other good grade of photometer, photoelectric or visual, may be used.

REPORT OF CASES

In addition to the findings reported in the above case, 40 histories were obtained of children with acrodynia and their urine specimens were analyzed for mercury. These histories are summarized in table 1.

COMMENT

Urinary Mercury Excretion of Acrodynic and Control Persons.—In the following table 41 children are briefly reported on for whom a clinical diagnosis of acrodynia was made. Mercury was found in the urine of 38, or 92.7 per cent, of these children. For most patients several examinations of urine were made, and as a rule mercury was found repeatedly and the values remained in the same range for some time. However, occasionally in the same patient the excretion of mercury varied greatly from sample to sample, and sometimes a urine specimen was free of mercury or contained very small amounts, although before and afterward appreciable quantities were recovered. Presence of mercury in the urine, particularly if proved repeatedly, indicates previous exposure to mercury. When mercury is absorbed through the skin, the intestinal or respiratory tract or from tissues into which it was injected, elimination from the body begins within a short time; it has been discovered one-half hour after administration.[12] Excretion proceeds rapidly in some cases and slowly in others. According to Lomholt,[12] the mercury is carried through the blood straem to all tissues of the body, but it is

11. Hubbard, D. M.: Determination of Mercury in Urine, Indust. & Engin. Chem. (Anal. Ed.) **12**:768, 1940.

12. Lomholt, S.: Quecksilber, theoretisches, chemisches und experimentelles, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1928, vol. 18, p. 1.

TABLE 1.—*Summary of Data on Series of Children with Acrodynia*

Case No.	Age and Sex	Outline of Clinical Course of Acrodynia	Urinary Mercury, Micrograms per Liter	Source of Mercury	Dimercaprol* Treatment	Outcome
2	2 yr. M	Lacrimation, anorexia, irritability, pain, sleeplessness; recurrent rash; later excessive perspiration, pink palms and desquamation; difficulty in voiding, muscles flabby and reflexes absent; blood pressure 150/80; duration about 4 mo.	160 20 180 (4th mo. of disease)	Unknown	None	Improved
3	3 yr. M	Anorexia, photophobia, irritability; refused to walk and play; hands cold, wet and peeling; blood pressure 120/80	45 24 (3d and 4th mo. of disease)	Unknown	None	Slow improvement
4	13½ yr. M	Acrodynia at age of 2½ yr.; when 8 yr. old had muscular weakness; muscular fibrillary twitchings, irritability, hot, itching extremities; acrodynia, progressive muscular atrophy and heavy metal poisoning were considered in the differential diagnosis; when 13 yr. old patient had anorexia, diarrhea, warm and tender feet, muscular weakness and muscular twitching, burning sensations; patient had been pronounced sensitive to mercury by his physician after treatment with merbromin (see p. 000)	6 0 (On 3d admission)	Unknown	None	No improvement
5	3½ yr. F	Anorexia, loss of weight, weakness, papulopustular rash, photophobia, tachycardia; blood pressure 104/64	90 10 (In 2d mo. of disease)	Unknown	None	Gradual improvement
6	3 yr. M	Abdominal pain, cold and painful hands and feet, irritability, anorexia, perspiration, pruritic eruption, tachycardia; blood pressure 120/90	100 130 (6th wk. of disease)	(?) (Had received treatment for pinworms)	None	Rapid improvement
7	7½ mo. F	This case was reported in detail by Elmore [123]	80 (3 mo. after administration of teething powders) 60 120 (After BAL treatment)	Calomel-containing teething powders	+	Improved
8	9 mo. M	This case was reported in detail by Elmore [123]	430 (1 mo. after administration of teething powders)	Calomel-containing teething powders	+	Improved
9	11 mo. M	Listlessness, drowsiness, anorexia, pruritic rash; kept face buried in pillows; perspiration, increased salivation, pain in the mouth, desquamation, muscular weakness; tachycardia; blood pressure 118/80	80 50 40 (1 mo. after onset of disease)	Unknown	None	Slow improvement
10	3 yr. M	Irritability, anorexia, rash, cold extremities, flaccid muscles, loss of weight; blood pressure 120/84	14 72 40 0 (In 2d mo. of disease) This boy secreted mercury in the urine 7 mo. after clinical recovery from acrodynia	5% ammoniated mercury ointment for impetigo 4 wk. before onset of acrodynia	None	Improved 6 wk. after onset of disease
11	10 mo. M	Irritability, anorexia, excessive perspiration, sleeplessness, loss of weight; tachycardia, blood pressure 114/82; muscular hypotonia, fine rash	300 300 (2 mo. after onset of disease) Mercury secretion, 30 to 420 micrograms per liter continued during BAL treatment	Unknown	+	Improved
12	7 mo. F	Irritability, excessive perspiration, photophobia, muscular weakness	160 (1 mo. after administration of teething powder)	Calomel-containing teething powders	None	Unknown

* According to the criteria of Bivings and Lewis.[116c] Plus sign indicates dimercaprol treatment was given.
† R indicates adverse reaction to treatment with dimercaprol.
‡ This case was reported by Beale and Schrum.[120]
§ See pages 358 and 359 of text and Lelong, M., and Odinet, J.: Bull. Soc. pediat. de Paris **28**: 12, 1930, and Popovicin, G., and Pop, O.: Ann. pediat. **158**: 25, 1946.

TABLE 1.—*Summary of Data on Series of Children with Acrodynia—Continued*

Case No.	Age and Sex	Outline of Clinical Course of Acrodynia	Urinary Mercury, Micrograms per Liter	Source of Mercury	Dimercaprol* Treatment	Outcome
13	1 yr. F	Irritability, anorexia, itching and cold hands, muscular weakness, excessive perspiration; tachycardia, blood pressure 110/90; rash; complicated by pneumonia	300 300 (2 wk. after admission)	Unknown	+	Death
14	19 mo. M	Irritability, anorexia, red, itching hands and feet, desquamation; kept eyes protected from light; muscular hypotonia; tachycardia, blood pressure 120/60	260 400 (3 mo. after onset of disease)	Unknown	None	Improved
15	11 mo. M	Fever, morbilliform rash, conjunctivitis; kept head between his feet and chewed his fingers; anorexia, diarrhea, loss of weight, perspiration, swollen gums, ulcerated tongue, flaccid muscles	300 360 (5 mo. after administration of teething powders)	Calomel-containing teething powders (1 mo. before appearance of symptoms)	+	Slow improvement
16	9 mo. M	Macular rash, photophobia, red hands and feet, excessive perspiration, anorexia, restlessness, sleeplessness; rubbed his hands and feet; became progressively weaker	40 (At time of clinical improvement)	Calomel-containing teething powders several mo. before onset of illness	+ (R) †	Rapid improvement
17	8 yr. F	Had red, painful hands and feet and intermittent rash over the body for 3 yr.; blood pressure 142/102; was improved when urine specimens were taken	0 0 (In 3d yr. of disease)	Unknown	None	Unknown
18	13 mo. F	Papular rash, hands and feet red and clammy, irritable, restless, sucked her hands, desquamation	240 (1 mo. after onset of disease)	Unknown	None	Unknown
19	10 mo. M	Photophobia, irritability, excessive perspiration, anorexia, burrowed head in pillow, rash, red hands and feet; systolic blood pressure 120	70 (1 wk. after onset of disease) 80 20 35 (After BAL treatment)	Calomel-containing teething powders (1 wk. before onset of symptoms)	+	Slow improvement
20	1 yr. M	Malnutrition, excessive perspiration, rash; rubbed hands and feet which were red and peeling; photophobia; tachycardia, blood pressure 150/110	50 280 580 (In 3d mo. of disease)	Ammoniated mercury ointment for eczema (1 mo. before onset of illness)	None	Improved
21	15 mo. F	Fretful, limp, eyes red and sensitive to light; morbilliform rash, nose red and cold, palms pink and clammy	17 30 40 (2 wk. after onset of disease)	Calomel-containing teething powders (symptoms appeared immediately after second administration)	+	Improved rapidly
22	10 mo. F	Restless, irritable, knocked her head; muscular hypotonia, palms and soles moist and cool; tachycardia, blood pressure 160/104	280 140 (2 days after BAL treatment was begun)	Calomel-containing teething powders given for 10 wk.; symptoms present 2 mo. later	+	Improved rapidly (except for hypotonia)
23	20 mo. M	Restless, rash on hands and feet which were cold, itching and peeling; tachycardia, blood pressure 130/90	720 30 30 (After BAL treatment)	Calomel-containing teething powders	+ (4 days only)	Improved
24	6 mo.	Photophobia, anorexia, general weakness	330 210 50 (At times of examination)	Calomel-containing teething powders (given for 2 mo. before examination)	+	No marked improvement
25	14 mo. F	Irritability, photophobia, rash, toes pink and cold, chewed and rubbed hands, ceased walking; tachycardia, blood pressure 156/110	110 90 (5 and 6 wk. after onset of symptoms)	Unknown	None	Rapid improvement
26	15 mo. F	Anorexia, loss of weight, rash, refused to walk, hands and feet red and itching; loss of teeth, insomnia; tachycardia, blood pressure 134/104 ‡	370 100 (4 and 8 wk. after onset of symptoms)	Unknown	+ (R) (R) †	Gradual improvement
27	1 yr. M	Scarlatiniform rash, desquamation, anorexia, listlessness, flaccid muscles, red, itching fingers, extremities hypotonic, tremor, excessive perspiration, loose teeth, voluntary voiding impossible, inability to cough and swallow; after autopsy 2.77 mg. of mercury per 100 Gm. found in kidneys; tachycardia, blood pressure 140/90; spinal puncture: no cells, 237 mg. of protein per 100 ml.§	120 20 10 (2 mo. after onset of symptoms)	Diapers rinsed in mercury bichloride (2 mo. before onset of illness)	+	Death

TABLE 1.—*Summary of Data on Series of Children with Acrodynia—Continued*

Case No.	Age and Sex	Outline of Clinical Course of Acrodynia	Urinary Mercury, Micrograms per Liter	Source of Mercury	Dimercaprol* Treatment	Outcome
28	4 yr. M	Abdominal pain, convulsions, extremities itching, painful and cold, excessive perspiration, irritable, assumed peculiar positions; tachycardia, blood pressure 140/90	58 85 (6 wk. after onset of symptoms)	Santonin-calomel treatment for worms (4 mo. before onset of symptoms)	+	Rapid improvement
29	20 mo. M	Irritability, anorexia, insomnia, redness of palms and soles, tachycardia, blood pressure 180/120, rash; child assumed peculiar positions; glycosuria	230 200 140 (2 and 3 wk. after onset of symptoms)	Calomel-containing worm pills (2 wk. before onset of symptoms)	+	Gradual improvement
30	2 yr. M	Anorexia, hands and feet red, swollen and desquamating, photophobia, rash	40 80 110 (3 mo. after onset of symptoms)	Unknown	+	Improved
31	1 yr. ..	Irritable, slept poorly, excessive perspiration, photophobia, palms and soles red, muscles flaccid, desquamation, lost weight, tachycardia, blood pressure 120/80	10 30 100 (2 mo. after onset of symptoms)	Diapers rinsed in mercury bichloride (6 wk. before onset of symptoms)	None	Gradual improvement
32	1 yr. F	Restlessness, anorexia, rash, perspiration, photophobia, desquamation, systolic blood pressure 150	80	?Calomel tablets (3 mo. before onset of symptoms)	None	Gradual improvement
33	3½ yr. F	Stiffness of neck, inability to walk, irritability, generalized pain, hands and feet red and swollen, tachycardia, blood pressure 140/100; spinal fluid: 100 mg. of protein per 100 ml. and 17 cells (13 lymphocytes)	25	Unknown	+	Unknown
34	7 mo. F	Photophobia, restlessness, thrashed her head about, muscular hypotonia	70 (2 wk. after onset of symptoms) 2,430 (On 4th day of BAL treatment) 1,430 190 (4 wk. later)	Calomel-containing teething powders (for 4 mo. before onset of symptoms)	+	Gradual improvement
35	9 mo. M	Irritability, hands cold and red, slight photophobia, diaper rash, blood pressure 140/110	1,660 (Before BAL treatment) 1,040 390 (After BAL treatment)	Diapers rinsed in mercury bichloride 1½ mo. before outbreak of symptoms	+	Improved
36	2 yr. M	Anorexia, irritability, loss of weight, rash; hands and feet beefy red, itching and desquamating, excessive perspiration	160 90 (5 wk. after onset of symptoms)	Calomel several mo. before onset of symptoms	+	Slow improvement
37	16 mo. F	Anorexia, irritability, insomnia, perspiration, photophobia, muscular weakness, salivation, red and itching hands and feet, rash, blood pressure 140/115	120 140 (Several wk. after onset of symptoms)	Calomel (several wk. before appearance of symptoms)	+	Improved
38	13 mo. F	Photophobia, assumed bizarre positions, rash, chewed her fingers and toes which were pink; tachycardia, blood pressure 140/90	40 45 (Several mo. after onset of disease)	Calomel-containing teething powders	None	Slow improvement
39	6½ mo. M	Irritability, photophobia, paroxysms of pain, salivation, tachycardia, muscular hypotonia, rash	90 300 (3 mo. after onset of symptoms) 100 120 (6 mo. after use of diaper rinse)	Diapers rinsed in mercury bichloride	None	Slow improvement
40	5 yr. F	Irritability, hyperesthesia in hands and feet which were red, could not sleep, blood pressure 120/82, tachycardia, loss of upper central incisors	0 10	Thimerosal (†)	+	Improved
41	2 yr. F	Abdominal pain, excessive perspiration, rash, convulsion, assumed bizarre positions, muscular hypotonia, palms and soles pink	45 (6 wk. after onset of symptoms)	Santonin-calomel tablets for "worms"	+	Improved

deposited in the various tissues in different concentration. The kidneys and the liver usually show the highest mercury content per 100 Gm. of tissue, while the concentration in the blood is low. The metal is excreted from the tissues into the urine, bile, feces, sweat, saliva and milk. Urine apparently contains the largest amounts, but excretion is frequently irregular and interpretation of variations difficult. The amounts excreted are not necessarily indicative of the amounts ingested or resorbed, since factors such as ability of the tissues to store and release mercurial compounds influence urinary excretion.

It was not possible in our cases to find a correlation between the amounts excreted and the severity of the disease or to predict from these amounts how long the excretion would continue. In case 10, for example, only 14 micrograms per liter was found in the first urine sample but the child continued to excrete mercury for nine months. In some cases of known exposure and of severe manifestations occasional samples were free of mercury or contained only minimal amounts. For instance, when adverse reactions result from touching a funnel through which mercury has passed [13] or the fragments of a broken thermometer, measurable amounts of mercury probably will not be excreted. In one fatal case (case 27) only small amounts were found in the last urine specimens before death, although large quantities of mercury were observed to be stored in the kidney. Thus, excretion of mercury in the urine is a reliable sign of exposure to mercury, but in exceptional cases the urine may be free of measurable amounts in spite of exposure.

In table 2, part A, the results of the mercury determinations on the first urine specimens obtained from acrodynic patients and from control persons are compared. In table 2, part B, the results of all examinations are listed for the two groups.[14] In the acrodynic patients determinations were repeated oftener than in the control persons. Therefore, the results for the two groups as listed in table 2, part B, are not entirely comparable. It was thought preferable to record separately the results on the first samples obtained from each acrodynic patient and control person and to compare them.

Both parts of the table show a striking difference between the acrodynic and the control groups. While mercury was found in the first urine specimens in 92.7 per cent of the patients with acrodynia, 85 per cent of the control persons had no mercury in the urine. Only small amounts of mercury were obtained in the remaining control specimens of urine. In eight control urines values of 1 to 50 micrograms per liter were found; in four of these the mercury content was 10 micrograms per liter which is near the limit of error of the method. In three control children whose urine contained 40, 35 and 20 micrograms per liter, respectively, the source of mercury was found in thimerosal (merthiolate®), merbromin (mercurochrome®) and meralluride (Mercuhydrin) administered in the hospital at various times before the examination of the urine. One child excreted 70 micrograms per liter; on reexamination mercury was found in four additional samples (40, 80, 25 and 30 micrograms per liter). It was established that he had been given 10 tablets containing 6.5 mg. of mild mercurous chloride U. S. P. (calomel) each by a physician some time before the urine specimens were obtained. In one

13. Bass, M. H.: Idiosyncrasy to Ammoniated Mercury, J. Mt. Sinai Hosp. **10**:199, 1943.

14. In table 1 not all mercury determinations performed on the urine of the individual patients are listed.

child whose urine contained 30 micrograms of mercury per liter the source of mercury could not be ascertained. Thus, 91.7 per cent of the first control specimens were free of mercury or showed it in negligible amounts. In 8.3 per cent small but measurable amounts were found. The last group is of interest, since it demonstrates that children can remain free of acrodynia, although they receive, absorb and excrete mercury.

These results are in good agreement with those of our first publication[15] in which we stated:

> The fact that mercury is excreted in the urine of many children with acrodynia suggests that in small children a causal relationship may exist between exposure to and resorption of mercury and the symptom complex of acrodynia. The fact that after mercury medication children may excrete mercury in the urine in appreciable amounts without developing acrodynia suggests that an individual susceptibility (idiosyncrasy) to mercury intoxication exists in the children who develop acrodynia.

TABLE 2.—*Results of Urinary Determinations of Mercury*

A. Mercury Content of First Urine Specimens Obtained from 41 Acrodynic and from 60 Control Persons

Mercury in the Urine, Micrograms per Liter	Number of Acrodynic Persons	Number of Control Persons
Over 400	4	0
301 to 400	3	0
201 to 300	7	0
101 to 200	6	0
51 to 100	8	1
1 to 50	10	8
0	3	51
Total	41	60

B. Mercury Content of All Urine Specimens Obtained from 41 Acrodynic and from 60 Control Persons

Mercury in the Urine, Micrograms per Liter	Number of Acrodynic Samples	Number of Control Samples
Over 400	12	0
301 to 400	7	0
201 to 300	19	0
101 to 200	40	0
51 to 100	42	2
1 to 50	62	14
0	7	71
Total	189	87

Hypersensitivity and Idiosyncrasy to Mercury: Variation of Tolerance.—From the foregoing sections there is good evidence that children with acrodynia were in most instances exposed to mercury before outbreak of the disease. It will be shown in a later section that acrodynia and mercury poisoning have many symptoms in common. However, most of our knowledge of mercury poisoning has been obtained through observation of persons who displayed toxic symptoms after exposure to large amounts of mercury, and it remains to be explained why children who received small and generally well tolerated doses of mercurial medication have signs of intoxication. It will be difficult to convince physicians who have prescribed mercurial preparations in conventional doses for many years or persons who "have

15. Warkany, J., and Hubbard, D. M.: Mercury in the Urine of Children with Acrodynia, Lancet **1**:829, 1948.

been raised on calomel" of the mercurial origin of acrodynia. However, the fact that a chemical substance, organic or inorganic, is tolerated by "most of the people most of the time" does not rule out the possibility that it can bring about pathological manifestations in specific cases. It does not seem necessary to enumerate special instances of idiosyncrasy and hypersensitivity to illustrate this point. Just as some persons react with asthma or hay fever to environmental conditions well tolerated by others, so some children may react adversely to small amounts of mercury which may be beneficial to others.

It is known that tolerance to mercury varies enormously. This variation in tolerance is one of the factors responsible for the opposition to mercurial drugs which existed in many forms as "antimercurialism" ever since mercury was introduced into occidental medicine as the most effective treatment against syphilis. It was observed repeatedly that mercurial drugs, though prescribed in customary amounts and with customary precautions, would produce deleterious effects. One of these unfortunate incidents was candidly described in 1865 by Underwood,[16] who observed fatal gangrene of the mouth in several children following administration of small amounts of mild mercurous chloride (see p. 353). The outstanding toxicologist, Lewin,[17] who will be cited repeatedly in the subsequent discussion, stated in 1893 that idiosyncrasy may exist to the smallest dose of mercurial compounds. Individual conditions, together with the amount of the preparation taken, determine the severity of toxic side effects. There are persons who can be given mercury in almost any amount without the development of stomatitis, while others will exhibit oral complications after ingestion of as little as 0.05 Gm. of mild mercurous chloride or after inunction with mild mercurial ointment (blue ointment) for pediculosis pubis. Temporary or individual circumstances may cause side effects in various ways. Some children who react adversely to moderate doses of mild mercurous chloride may acquire serious stomatitis and die.[18] Mercurial inunctions, used for the treatment of syphilis, may occasionally cause severe adverse reactions. Some of these can be attributed to overdose or lack of oral hygiene, but others have developed in patients treated according to standard technics. Rashes, stomatitis and intestinal symptoms have been observed. According to Lewin, children frequently react to mild mercurial ointment with stomatitis and enteritis, and since treatment with this substance has sometimes caused a fatal outcome the old physicians advised using it for children only with caution. This statement is of great interest as the newer pediatric textbooks neglect to mention adverse side effects of mercurial inunction treatments for congenital syphilis. In recent pediatric publications hypersensitivity to mercury has been reemphasized. Jenny[19] described rashes in children who received mild mercurous chloride in doses customary for the eradication of worms. Harper[20] reported two cases of idiosyncrasy to ammoniated mercury ointment which showed some resemblance to

16. Underwood, A. L.: Mercurial Gangrene, Cincinnati Lancet & Observer **8**:585, 1865.

17. Lewin, L.: Die Nebenwirkungen der Arzneimittel, Berlin, A. Hirschwald, 1893.

18. (*a*) Lewin.[17] (*b*) Leschke, E.: Clinical Toxicology, Baltimore, William Wood & Company, 1934.

19. Jenny, E.: Ueber Quecksilberexantheme bei Kindern, Schweiz. med. Wchnschr. **60**: 942, 1930.

20. Harper, P.: Idiosyncrasy to Ammoniated Mercury Ointment, J. Pediat. **5**:794, 1934.

acrodynia. Gibel and Kramer [21] observed acute idiosyncratic reactions to 5 per cent ammoniated mercury and to mercury bichloride used as a diaper rinse. Similar adverse reactions were reported by Bass [22] following the administration of mild mercurous chloride (½ grain [0.03 Gm.]), ammoniated mercury and yellow mercuric oxide ointments, the use of a soap containing mercury bichloride and contact with traces of metallic mercury. Fanconi, Botsztejn and Schenker [23] observed 56 cases of untoward reactions to mercury in hypersensitive children, 39 of which were "calomel disease." These examples illustrate that some persons have a lower tolerance to mercury than others and that they may react to small amounts of mercury with a variety of pathological manifestations, such as skin rashes, stomatitis, gangrene of the mouth, calomel disease and others. If this is admitted, it should not be too difficult to accept the possibility that in exceptional cases children may react to small amounts of mercury by displaying the symptoms implied by the name "acrodynia." The concept is the more plausible since many symptoms of acrodynia, as will be shown, have also been observed in cases of mercury poisoning.

We have expressed the belief that an individual susceptibility (idiosyncrasy) to mercury intoxication exists in children who have acrodynia. The use of the word "idiosyncrasy" in this connection demands clarification, since the term has different connotations. Sometimes idiosyncrasy is considered to be a congenital and even inherited susceptibility that stays with the person throughout life. Families are known in which such an idiosyncrasy to mercury was apparently passed on from parent to child.[24] If this type of idiosyncrasy were the basis of acrodynia, one would expect that patients who have had acrodynia once will have it repeatedly or show other adverse reactions whenever they come in contact with mercurial compounds. Since there is no evidence that patients who recover from acrodynia always remain sensitive to mercury and since recurrence of acrodynia is the exception rather than the rule, we are obviously not dealing with a permanent idiosyncrasy in acrodynic patients. Clinical experience had shown that tolerance to mercury increases in some patients while it decreases in others.[25] Tomasczewski [26] desensitized a syphilitic patient who had reacted adversely to mild mercurous chloride, mild mercurial ointment and mercury injections by cautious administration

21. Gibel, H., and Kramer, B.: Idiosyncrasy to Mercury Preparations in Childhood, Am. J. Dis. Child. **66**:155 (Aug.) 1943.

22. (*a*) Bass.[18] (*b*) Bass, M. H.: Idiosyncrasy to Ammoniated Mercury Ointment in Childhood, Urol. & Cutan. Rev. **45**:78, 1941; (*c*) Idiosyncrasy to Metallic Mercury, with Special Reference to Amalgam Fillings in the Teeth, J. Pediat. **23**:215, 1943.

23. Fanconi, G.; Botsztejn, A., and Schenker, P.: Überempfindlichkeitsreaktionen auf Quecksilbermedikation im Kindesalter mit besonderer Berücksichtigung der Calomelkrankheit, Helvet. pædiat. acta (supp. 4) **2**:3, 1947.

24. (*a*) Jenny.[19] (*b*) Bossard, G.: Ueber seltene Formen der Quecksilbervergiftung mit besonderer Berücksichtigung der Exantheme nach innerlicher Anwendung, Dermat. Ztschr. **4**: 50, 1897. (*c*) Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, Philadelphia, Lea & Febiger, 1947, p. 187.

25. Almkvist, J.: Quecksilberschädigungen, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, J. Springer, 1928, vol. 18, p. 178.

26. Tomasczewski: Quecksilber-Idiosynkrasie und Gewöhnung, Arch. f. Dermat. u. Syph. **67**:139, 1903.

of increasing doses of mercury. Such desensitization sometimes occurs spontaneously, and Bossard [24b] encountered patients who responded to the first exposure to mercury with severe rashes but showed milder or no symptoms after repeated exposures. Stock,[27] on the other hand, emphasized the hypersensitivity found among laboratory workers, industrial workers, physicians and dentists which is always acquired by repeated exposure. The question of sensitization and desensitization to mercury was discussed by Fanconi, Botsztejn and Schenker [23] in connection with their description of calomel disease. According to these authors, most children remain well after exposure to mercury or may react to it subclinically and acquire a "silent immunization." Other children react by having calomel disease, an acute febrile and exanthematous disorder which begins about eight days after ingestion of mild mercurous chloride and lasts as a rule only a few days. Recovery from calomel disease leaves the child, in the majority of cases, with a certain immunity to mercury. This was demonstrated in the observation that mercurial skin reactions (Bloch's patch test) were usually strongly positive in the first few days of calomel disease, became less pronounced in the following days and were negative in the second week of the disease. An attempt to produce a second attack of calomel disease in some children elicited no reaction. In rare instances a child may retain his sensitivity to mercury following recovery from calomel disease and respond after reexposure with a second attack of the disease. Recently, Baumann [28] published a report on five cases of calomel disease.

These citations will suffice to show that hypersensitivity to mercury may change with or without a clinical reaction and may give way to an "immunity" or a tolerance to mercurial preparations. It appears that acrodynia is one of the clinical manifestations shown by hypersensitive children after exposure to mercury. Recovery from acrodynia seems to leave most children with a normal tolerance to mercury, but occasionally sensitivity may persist and acrodynia recur.[29] Péhu [29f] was of the opinion that the second illness is, as a rule, milder than the first, an observation which might be explained on the basis of an incomplete "immunity" acquired by the first attack.

The fact that only a small number of hypersensitive children respond to mercurial medication has obviously delayed recognition of the causal connection between exposure to mercury and acrodynia. Another factor is the variability of the interval between the administration of the drug and the onset of the disease. In our series the interval varied from one week to several months. Similar observations were

27. Stock, A.: Die chronische Quecksilber- und Amalgam-vergiftung, Arch. f. Gewerbepath. u. Gewerbehyg. **7**:388, 1936.

28. Baumann, T.: Calomel-Krankheiten, Schweiz. med. Wchnschr. **79**:725, 1949.

29. (*a*) Debré, R., and Cléret, H.: Acrodynie infantile à forme mutilante: Récidive d'acrodynie après 7 années d'intervale; Séquelles psychiques et vaso-motrices, Bull. Soc. pédiat. de Paris **30**:314, 1932. (*b*) Deuber, A.: Klinische Beiträge zur Neurose des vegetativen Nervensystems (Selter-Swift-Feer), Schweiz. med. Wchnschr. **58**:529, 1928. (*c*) Zahorsky, J.: Recurrences of Acrodynia: Report of a Case, Arch. Pediat. **60**:483, 1943. (*d*) Weill-Hallé, B.: Un cas d'acrodynie récidivante: Étude du syndrome vaso-moteur, Bull. Soc. pédiat. de Paris **32**:447, 1937. (*e*) Eschbach, H.: Acrodynie, chorée fibrillaire et symptômes encéphalitiques, Bull. et mém. Soc. méd. d. hôp. de Paris **61**:338, 1945. (*f*) Péhu, M.: Les récidives de l'acrodynie infantile, Schweiz. med. Wchnschr. **71**:1207, 1941.

made by Fanconi and Botsztejn.[30] In a case described by Keller [31] in 1925 mercury bichloride washes preceded the outbreak of acrodynia by three months. In mercurial polyneuritis the interval between the beginning of mercurial treatment and the onset of the disease varied from 10 days (case 1 [32]) to several months.[33] It is not easy to combine the assumption of hypersensitivity in children who display acrodynia with the observation of a long interval between administration of the drug and outbreak of the disease. However, even in cases of "idiosyncrasy" to mercury [34] the interval between the first application of the ointment and the onset of the reaction varied from one to 20 days. Underwood [16] was puzzled by the fact that mercurial gangrene of the mouth developed 12 days after administration of a small dose of mild mercurous chloride; in recent years Oppikofer and Fehrenbach [35] observed six months after discontinuance of the use of mercurial diuretics recurrences of mercurial stomatitis with necrotic changes causing death by hemorrhage from the lingual artery. In a patient of Gwalter [36] mercurial pemphigus and gangrene of three fingers appeared two months after use of a mercurial ointment. Lewin [17] pointed out that after injections of mercury compounds the metal is deposited in some insoluble form in the body. For reasons unknown the depot may become soluble and then produce inflammatory or gangrenous changes in the mouth or pharynx. How long mercury may persist in the organism is well demonstrated by the duration of its excretion in the urine in some of our cases, and after antisyphilitic treatment mercury has been demonstrated in the urine several years after the last administration.[12] What are then the accessory factors that produce sudden toxicity in some persons from the harmless mercury compounds which are present in every organism after exposure to mercury?

Much thought has been given in the past to the changes in tolerance to mercurial preparations. At first it was believed that all adverse reactions to mercury could be attributed to overdosage, but adverse reactions were not eliminated entirely by the administration of moderate doses. Mild mercurous chloride was considered dangerous when it stayed in the intestinal tract for any length of time because it was thought that it might be converted into the poisonous mercury bichloride if it was not eliminated promptly. Therefore, physicians prescribed saline laxatives or castor oil after the administration of mild mercurous chloride to assure prompt

30. Fanconi, G., and Botsztejn, A.: Die Feersche Krankheit (Akrodynie) und Quecksilbermedikation, Helvet. pædiat. acta **3**:264, 1948.

31. Keller, W.: Ein Beitrag zur Kasuistik der kürzlich von Feer beschriebenen vegetativen Neurose im Kindesalter, Klin. Wchnschr. **4**:1256, 1925.

32. Spillmann, P., and Étienne, G.: Polynévrites dans l'intoxication hydrargyrique, aiguë ou subaiguë, Rev. de méd., Paris **15**:1009, 1895.

33. (*a*) Gilbert, W. H.: Pseudotabes mercurialis, Deutsche med. Wchnschr. **20**:842, 1894. (*b*) Forestier, H.: Polynévrite motrice des membres, d'origine mercurielle, Méd. mod. **1**:425, 1889-1890.

34. (*a*) Bass.[18] (*b*) Harper.[20] (*c*) Gibel and Kramer.[21] (*d*) Wilbar, C. J., Jr.: Mercury Poisoning from Topical Application of 15 per cent Ammoniated Mercury, J. Pediat. **20**:89, 1942.

35. Oppikofer, E. K., and Fehrenbach, H.: Ueber Stomatitis mercurialis ulcerosa und Kiefernekrose nach Anwendung der Quecksilberdiuretika (Salyrgan, Esidron), Schweiz. med. Wchnschr. **76**:983, 1946.

36. Gwalter, E.: Ein Fall von Quecksilbervergiftung, Zurich, O. Füssli u. Comp., 1877; cited by Bossard.[24b]

expulsion of the mercurial compound. However, when mild mercurous chloride is given concealed in teething powders, in worm candy or in tablets containing other ingredients, this safety measure may be neglected, and one will have to consider the possibility that adverse reactions, such as acrodynia or calomel disease, may result in part from insufficient elimination of the drug. While this may play a role in the causation of adverse effects, saline purgation does not seem to prevent the accidents infallibly. Underwood [16] emphasized that gangrene of the mouth occurred in his patients in spite of saline catharsis. It was known that use of mild mercurous chloride is dangerous to patients with paralytic ileus or volvulus, nephritis, advanced pulmonary tuberculosis or anemia and to alcoholics.[37] None of these conditions was present in children who had acrodynia after administration of mild mercurous chloride.

Age is an outstanding predisposing factor to acrodynia. It is known that infants and small children up to the age of 4 years are more likely to acquire acrodynia and calomel disease [28] than older children. However, there are exceptions to this rule, and acrodynia can occur in older children and even in adults, while many small children are able to tolerate mercurial preparations. We do not know the real predisposing factor, which is present more frequently in younger children than in older children. In recent years it has been pointed out that persons who are sensitive to mercury are often allergic to other substances also, or that they have close relatives with allergic conditions.[38] This point deserves attention, but it will be necessary to demonstrate that a history of allergy is actually obtained oftener in acrodynic children than in a group of control children. The concept of allergy as a factor in the causation of acrodynia would be in agreement with the observation of occasional familial incidence in this disease, since allergic tendencies are often familial. However, familial incidence could also be explained by the similarity of treatment to which children of one family are likely to be subjected, such as periodical worm treatments, administration of teething powders, use of one mercurial ointment for any type of skin disorder or regular "purgations" with mild mercurous chloride. Deterioration of mild mercurous chloride or of other mercurial compounds before administration must also be kept in mind. If in a certain area a supposedly insoluble mercurial compound was distributed in a somewhat soluble form, or if solubility was facilitated by the addition of other drugs to the powder or tablet containing mild mercurous chloride, toxic effects could make their appearance repeatedly in that region. This factor, as well as regional custom in the use of mercurial preparations, may explain the endemic occurrence of acrodynia in certain areas. While all these factors may play a role in the causation of acrodynia, it must be emphasized that we are still ignorant of the decisive factor which makes mercurial preparations in conventional doses dangerous to a minority of children. We are not yet able to predict which child will tolerate mild mercurous chloride or ammoniated mercury (white precipitate) ointment and which will respond to it by showing acrodynia or some other adverse reaction.

Comparison of Symptoms of Acrodynia with Those of Mercury Poisoning.—We realize fully that an identity of groups of symptoms in a disease of unknown

37. (*a*) Lewin.[17] (*b*) Hamilton, A.: Industrial Poisons in the United States, New York, The Macmillan Company, 1925.

38. Fanconi and others.[28] Stock.[27]

cause and a disorder of known origin cannot per se constitute evidence in favor of the same causative factor operating in both conditions. Nevertheless, the data already presented in this communication provide a cogent independent reason for believing that sensitivity to mercury is the important etiological factor in many and perhaps most cases of acrodynia. The circumstance rendered it important to examine carefully the diversified symptomatologies of both acrodynia and mercury poisoning. The parallelism among groups of symptoms which has been discovered furnishes supportive evidence for belief in the direct evidence of the role of mercury in the causation of acrodynia.

Acute mercury poisoning as it is seen in persons who take large doses of mercury bichloride by mouth or absorb it in large amounts by some other means is characterized by violent gastrointestinal symptoms as well as by typical renal changes. We do not have to discuss these acute symptoms of mercury poisoning here because they have little in common with acrodynia. However, manifestations of subacute mercury poisoning which follow the acute phenomena and of chronic mercury poisoning as seen in industries may resemble symptoms of acrodynia. Thus, stomatitis, salivation, loosening and loss of teeth, necrosis of the jawbones, muscular weakness, tachycardia, colitis, tenesmus, ulceration of the intestine, hemorrhagic phenomena, dermatitis and polyneuritis may appear several days or weeks after ingestion of a mercurial poison or of an overdose of a mercurial drug. Similar symptoms have been observed in industrial workers after various periods of exposure to mercury.[39] In the following paragraphs we have given brief descriptions of the symptoms of acrodynia as they appear in various organs and compared them to manifestations of mercury poisoning.

Cutaneous Manifestations: Morbilliform, scarlatiniform, urticarial, miliary, vesicular and hemorrhagic rashes have been described in acrodynia. Pyodermic infections may be superimposed on such eruptions. In some cases rashes appear and disappear several times during the course of the disease, while in others skin eruptions are not prominent. The hands and feet are pink when warm or cyanotic when cold. They appear swollen and often show considerable desquamation, particularly the fingers and toes. Itching and burning are outstanding features of acrodynia. The skin shows signs of marked vasolability, and sometimes urticarial manifestations can be elicited by superficial scratching of the skin.[40] Perspiration is particularly excessive so that bedclothes become soaked, necessitating numerous changes. "Mothers frequently change the child's nightgown and bedding many times a day. There is no other disease of childhood that has such marked and continuous sweating as that which occurs in the course of a well-developed case of acrodynia." [1]

An extensive literature exists on mercurial cutaneous manifestations. As early as 1793 Benjamin Bell [41] pointed out that exanthem may follow internal as well as external administration of mercury. He knew that mercurial rashes took the

39. (*a*) Hamilton.[87b] (*b*) Neal, P. A., and others: A Study of Chronic Mercurialism in the Hatters' Fur-Cutting Industry, Public Health Bulletin 234, United States Treasury Department, Public Health Service, 1937.

40. Feer, E.: Die spezifische vegetative Neuropathie des Kleinkindes (kindliche Akrodynie), Schweiz. med. Wchnschr. **65**:977, 1935.

41. Bell, B.: Treatise on Gonorrhea Virulenta and Lues Venerea, Dublin, W. Jones, 1793.

form of macular, urticarial, erythematous or vesicular eruptions. He pointed out that burning and itching occurred in the course of these rashes. Many publications on this subject originated in the nineteenth century at a time that physicians had much more experience with mercurial drugs than they have now. Reviews of the older literature were made by Bossard [24b] and Almkvist.[42] In addition to the rashes described by Bell, scarlatiniform, erysipelatous, eczematous and pemphigoid rashes with subsequent desquamation were observed. A relatively mild reaction to mild mercurous chloride or other mercurial drugs takes the form of "measles." Such cases can be found in Bossard's review and in an article by Jenny.[19] In 1947 Fanconi, Botsztejn and Schenker [23] gave an excellent description of this mercurial disorder, which they called calomel disease. They considered a rash, fever, generalized adenitis with or without enlargement of the spleen, eosinophilia and relative leukopenia as the cardinal symptoms of the disease. The rashes may take various forms. In the beginning they are often scarlatiniform, but within a few hours they become morbilliform and urticarial or resemble megalerythema. The trunk, the face and the extremities can be affected at the same time. Desquamation may occur in the second week of the disease, but neither the palms nor the soles peel. There is little resemblance between calomel disease and acrodynia. Thus, Fanconi and his co-workers [23] and Baumann [28] pointed out that in some of their patients calomel disease was followed by typical acrodynic syndromes. Keller [31] and others described cases of acrodynia which were preceded by atypical measles or scarlet fever.

Many cases of mercurial dermatoses are acute and fulminant reactions to exposure to mercury. They are usually febrile and of short duration. They differ in these respects from acrodynia, but there are also certain points of resemblance. In fact, some of these cases may be considered acute acrodynia. Thus, in the case of Engelmann,[43] an adult who received three small doses of mild mercurous chloride noticed several hours later itching and light sensitivity of the eyes. Erythema and edema of the face and insomnia developed. The skin became red. He had a high fever. Four days later desquamation in large sheets set in. He recovered after two weeks. This man was very sensitive to mercury, and the attack described was his third following exposure to mercury. Similar cases of idiosyncrasy to mercury have been described in recent years in the pediatric literature.[44] Of special interest in this respect are the cases of Harper.[20] Although his patients were obviously sensitive and reacted to ammoniated mercury ointment with acute symptoms of short duration, the disease picture showed sufficient resemblance to acrodynia for the author to consider that disease first in the differential diagnosis. Wilbar's patient,[34d] who had an afebrile reaction to topical application of 15 per cent ammoniated mercury ointment, showed salivation, scaling and crusting of the skin and marked signs of pruritus. The hands and feet were moderately edematous and bluish. Some edema of the face and moderate scaling of the scalp were present.

---

42. Almkvist, J.: Ueber merkurielle Dermatosen: Klinische, histologische und experimentelle Studien, Arch. f. Dermat. u. Syph. **141**:342, 1922.

43. Engelmann, F.: Ein Fall von Erythema universale nach Gebrauch von Calomel, Berl. klin. Wchnschr. **16**:647, 1879.

44. Footnote 22. Harper.[20] Gibel and Kramer.[21] Wilbar.[34d]

An acute reaction to mercury, comparable to those just mentioned, was reported by Currie as "A Case of Erythroedema or 'Pink Disease'."[45]

This patient was given small doses of mild mercurous chloride for abdominal pain and constipation. On the following two days his condition became worse, and erythema developed on the chest and abdomen. He had a high fever, and the pulse rate was 140. His conjunctivas were injected, and he had photophobia. His tongue and lips were dry and sore. He displayed general weakness and muscular hypotonia; the tendon reflexes were absent. The tips of the fingers and toes were slightly reddened, swollen and painful to touch. On the following day he was semicomatose. The hands and feet were bright red, acutely tender and swollen. During the next two days, his temperature remained high and serious loss of weight and general weakness were noticeable. One week after the first dose of mild mercurous chloride the patient's condition began to improve, the temperature started to fall and the redness of the hands and feet became noticeable. From then on he improved daily. The hands and feet began to peel in large patches, and complete casts of some of the fingers were shed in one piece. Three weeks after commencement of the acute stage of the illness he was well except for the flabby condition of his leg muscles. There was no motor paralysis, but the tendon reflexes were still absent.

The author discussed the differential diagnosis and mentioned that the complete hypotonic state of the muscles suggested polyneuritis caused by intestinal toxemia. He did not mention the possibility of a mercurial origin for the disease. Since, however, comparable reactions of the skin to mild mercurous chloride have been described [46] and weakness of the muscles and hypotonia were observed in cases of mercurial polyneuritis (p. 360), it seems more likely that this boy had an acrodynic reaction to the mild mercurous chloride. The case represents a transitional form between the fulminant idiosyncratic and the protracted acrodynic reaction to mercury. A more typical case of acrodynia with a chronic course was described by Doig.[47]

The patient, whose disorder was reported as a case of "Pink Disease Occurring in an Adult," received mercurial treatment before onset of the symptoms, but the author did not associate them with the medication. This patient used a mercurial ointment in the treatment of pediculosis pubis and exhibited gingivitis soon afterward. He began to perspire profusely and persistently, and his hands and feet became red. He had pain in his hands and feet, with a burning sensation which was so severe that he could not sleep. He became anoretic and lost weight. His tongue was coated, and his breath was offensive. A generalized erythematous rash was present on the body, and the hands and feet were desquamating. His muscles were weak and flabby and had lost tone. A persistent coarse tremor was present in the muscles of the calf, the thighs and shoulder girdle. There was constant twitching of the toes. The patient was depressed and unable to sleep and presented an appearance of extreme misery. Tachycardia and eosinophilia persisted throughout the course of the disease which lasted several months.

This patient had protracted cutaneous manifestations and desquamation following mercurial medication. Like some patients with idiosyncratic reactions to mercury,[48] he had persistent eosinophilia. He had mercurial stomatitis with its typical offensive breath; he had mercurial polyneuritis and mercurial tremor. In addition he had profuse perspiration and tachycardia. This patient's disease can be labeled "acrodynia" as well as "mercury poisoning."

Excessive perspiration as a sign of mercury intoxication was known to Arabian physicians about 1,000 years ago.[25] Hyperhidrosis in chronic mercury poisoning

45. Currie, D. I.: Case of Erythroedema or "Pink Disease," Brit. M. J. **1**:48, 1928.

46. Bossard.[24b] Engelmann.[43]

47. Doig, K. M.: Pink Disease Occurring in an Adult, M. J. Australia **1**:782, 1938.

48. Harper.[20] Footnote 22 *b* and *c*. Currie.[45]

is mentioned by Hamilton [37b] and Reiselmann.[49] Veger [50] observed excessive perspiration in 56 per cent of workers in mercury industry, and Neal and his associates,[39b] studying chronic mercurialism in the hatter's fur cutting industry, observed the same symptom in workers who had other manifestations of chronic mercurialism. In a case of mercurial polyneuritis Spillmann and Étienne [32] described hyperhidrosis as an initial syndrome, stating that there appeared profuse sweats, at first during the night and later during the day and night.

Vasomotor lability, a symptom stressed by Feer [40] in acrodynia, was emphasized by Veger [50] and by Neal and others [39b] as a manifestation of chronic mercurialism.

Loss of hair occurs frequently in acrodynia and was observed in two of the first eight cases reported by Selter [51] in 1903. The hair becomes brittle and dull, changes color and falls out. In many instances the patients pull it out. Baldness of various degrees is often observed. Nutrition of the nails is also disturbed, and transverse lines may be found after the disease is over. In some cases the nails become brittle or discolored and drop off.

Loss of hair and nails may occur in persons after mercurial inunctions and the newly formed nails show thickening and furrows. Hamilton [37b] mentioned loss of hair in mercurial cachexia and Adler [52] in chronic mercury poisoning. A child reported on by Mayerhofer and Dragišić [53] who exhibited acrodynia following treatment with santonin and mild mercurous chloride, pulled his hair violently and showed beginning baldness. One of Keller's [31] patients who had acrodynia after mercury bichloride washes showed atrophy of the base of the nails, which could be lifted up so that the nail bed became visible.

Oral Manifestations: Salivation, stomatitis, loss of teeth and necrosis of the jawbones have been seen repeatedly in acrodynia. Bilderback [1] described the oral changes in the following way:

> One of the dramatic occurrences is the *loss of teeth*, sometimes all that have erupted. Frequently before any pathologic condition of the mouth has been recognized, a perfectly sound tooth will be found in the child's bed. Then it is noticed within a short time that the other teeth are becoming loose in their sockets and finally drop out. The mucous membrane of the mouth seems redder than normal and later becomes spongy and swollen. However, after the teeth are lost an infection may occur in the mouth with necrosis and shedding of the jaw bone for weeks afterward. At such times the mouth presents an appearance similar to ulcerative stomatitis; the gums are then swollen and ulcerated; saliva is profuse and the odor fetid.

This description summarizes very well the oral symptoms in severe cases of acrodynia. However, excessive salivation may occur in patients without stomatitis and represents one of the frequent symptoms of acrodynia. It was included by

49. Reiselmann, S. D.: Einfluss der Quecksilberintoxikation auf die ineren Organe, Arch. f. Gewerbepath. u. Gewerbehyg. **1**:496, 1930.

50. Veger, A. M.: Veränderungen des Nervensystems bei Arbeitern des Quecksilberbetriebes, Arch. f. Gewerbepath. u. Gewerbehyg. **1**:522, 1930.

51. Selter, O.: Trophodermatoneurosis, Arch. f. Kinderh. **37**:468, 1903.

52. Adler, L. H., Jr.: A Report of 5 Cases of Chronic Mercurial Poisoning, M. News **59**:186, 1891.

53. Mayerhofer, E., and Dragišić, B.: Neue Beiträge zur infantilen Akrodynie (Bericht über 41 Fälle), Arch. f. Kinderh. **113**:227, 1938.

Selter [54] among the cardinal symptoms of his trophodermatoneurosis as early as 1903. Necrosis of the tongue, the lips or the cheeks has also been described.[55]

The oral changes of acrodynia are typical of mercury poisoning. Almkvist [25] stated that the ancient inhabitants of India knew that "mercury separates the gums from the teeth, that the teeth become loose and salivation occurs." Arab writers of the ninth century after Christ knew that stomatitis, a fetid odor from the mouth and destructive ulcerations occur as oral complications of mercury medication. Mercurial ointments were used by Arab as well as European physicians against many chronic diseases before syphilis was brought to Europe. When mercury was employed against syphilis, its merits and demerits were discussed with great violence. The medical world became divided into "mercurialists and antimercurialists," and the latter knew of such complications as stomatitis and loss of teeth. The German knight, Ullrich von Hutton (1488-1523), who had himself undergone 11 inunction treatments with mercury ointments, could speak with particular authority about manifestations of mercury poisoning during antisyphilitic treatments:

> The patient after being anointed barely the second time began to grow weak in remarkable fashion: such was the violent effect of the ointment that it forced the disease which had been on the surface of the body into the stomach; thence it rose to the brain and thence flowed through the throat and mouth to such an extent and with such violent injury that the teeth fell out in the case of those who had not cared well for their mouths; at least in all cases the throat, tongue, and palate were ulcerated, the gums swelled, the teeth were loosened, sputum flowed without intermission through the lips with more stench than that of any foul matter and with such power of contagion that whatever it touched it immediately defouled and contaminated; whence the lips so touched contracted sores and the cheeks inside were infected. The whole house round about stunk and this type of treatment was so hard that many preferred to die of the disease rather than be cured in this way. . . . At length it came to such an unhappy stage that the use of the teeth was lost since they were loosened; and that besides the sick lost all appetite for food since the mouth was one great ulcer. . . .[56]

The manifestations of mercury poisoning were not forgotten during the centuries that followed. While mercurial antisyphilitic treatment was universally practiced, the antimercurialists were not silenced, and some of the symptoms of syphilis were attributed by them to treatment with the metallic ointment. While the earlier observers had knowledge of oral changes following exposure to huge doses of mercury, it was known to experienced physicians of the nineteenth century that some persons react to small doses of mercury with similar symptoms. In 1865 Underwood [16] wrote as follows:

> As regards the effect of calomel on the human system, a difference of opinion among medical men exists to some extent. With us all agree, however, that calomel when given in repeated doses for a long time, and when inflammatory effusions are taking place in the system, has a tendency to produce ptyalism. As the drug itself is supposed to produce a specific or peculiar kind of inflammation of an aplastic character, tending to ulceration and suppuration, evinced by a swelling and sponginess of the gums, and sometimes sloughing of the mucous

54. Selter, P.: Von "Acrodynie" bis "Encephalitis vegetativa": Die Geschichte einer Krankheit, Ergebn. d. inn. Med. u. Kinderh. **46**:315, 1934.

55. (*a*) Zahorsky, J.: Case of Erythroedema Complicated by Noma, Am. J. Dis. Child. **28**:261 (Aug.) 1924. (*b*) Woringer, P.: L'acrodynie infantile, Rev. franç de pédiat. **2**:440, 1926. (*c*) Zechlin, T.: Die Beziehungen der Selter-Swift-Feerschen Krankheit zu dem epidemischen Schweissfriesel (Sudo anglicus), Jahrb. f. Kinderh. **124**:195, 1929.

56. von Hutton, U.: Remarkable Medicine Guaiacum and Cure of Gallic Disease, Arch. Dermat. & Syph. **23**:409 (March); 681 (April); 1045 (June) 1931 (Reprint translated by C. W. Mendell).

tissues, gums and soft palate, frequently in severe cases a softening of the alveolar process and falling out of the teeth is witnessed. But the question to which I desire to call attention is, whether a moderate dose of calomel, say three grains, given to a patient four years old, of good constitution, clear of all apparent hereditary taint, and followed by saline or other active cathartics so as to produce a free evacuation of the bowels will, in ten days after its administration, produce "dry" gangrene of the mouth? Will calomel in any quantity remain latent in the system eight, ten or twelve days without any evidence of its presence, and then manifest itself in the form of gangrene, in its incipient stage on the tissues of the internal cheek? If so, does it not seem that the drug is a dangerous one in the hands of the practitioner, however cautiously administered, to children between two and five years old, and ought it not to be discarded as an internal remedy? Within the last three or four years several cases of gangrene of the mouth have occurred in this vicinity, which resulted in the death of the patients. . . .

Underwood himself had two patients of this type, and he called an older physician in consultation who apparently thought the gangrene was mercurial in origin, while Underwood considered it a manifestation of enteric fever for which it was administered. Jonathan Hutchinson was familiar with stomatitis caused by mercury-containing teething powders.[57] In 1893 Lewin[17] remarked in regard to side effects of mild mercurous chloride that temporal or congenital conditions may cause the occurrence of side effects in various ways and that there are children who react adversely to moderate doses of mild mercurous chloride, acquire stomatitis and die. Lewin knew of three degrees of mercurial stomatitis: Stomatitis simplex includes gingivitis, salivation, bad odor and metallic taste and stomatitis ulcerosa, the formation of ulcers of the gums, tongue, palate, cheeks and lips. There is salivation with fetid odor. The glands near the mouth are swollen. The teeth become loose and may fall out, particularly in children. Sometimes the entire face, especially the eyelids, are swollen. Sleep is disturbed, and the appetite disappears. Stomatitis gangrenosa, the third degree, involves destruction of large areas of the mouth, swelling of the tongue and necrotic changes of the bones of the mouth. Oral gangrene, which sometimes proceeds by leaps and bounds, may assume terrifying proportions in children, so that destruction of the entire lower half of the face is possible. The tongue may be destroyed, and the teeth may fall out. There is bleeding from the mouth, and the odor is fetid.

If these early authors had been confronted with cases of acrodynia complicated by severe oral manifestations, it is likely that they would have recognized the mercurial origin without benefit of urinary mercury determination.

Knowledge of mercurial gangrene was apparently almost but not entirely forgotten by pediatricians of the twentieth century. Dr. Carlton Watkins of Charlotte, N. C., has directed our attention to an early article on acrodynia by Zahorsky,[58] who wrote in 1922:

Still greater significance must be attached to the morbid changes occasionally found in the gums, when the hard alveolar process becomes soft, the teeth loosen in their sockets, and actually drop out one after the other, a phenomenon almost unknown in any other disease except poisoning from mercury or phosphorus.

And later, while discussing the causation of acrodynia, he stated:

For a time I was rather inclined to view the hypothesis of mineral poisoning with favor. Several of my patients had been given large doses of calomel at the onset of the disease,

57. Hutchinson, J.: Syphilis, Philadelphia, Lea Brothers Co., 1887.

58. Zahorsky, J.: Three Cases of Erythredema (Acrodynia) in Infants, M. Clin. North America **6**:97, 1922.

and the swollen gums, loosened teeth, with salivation, gave support to this. However, cases were encountered in which no history of calomel administration could be elicited, and this drug as a possible cause was dismissed.

Mercurial stomatitis in its most destructive form, with loss of teeth and sequestration of the alveolar processes, may be caused by the use of modern mercurial diuretics in customary doses.[58]

Manifestations on Other Mucous Membranes: Photophobia and lacrimation are early symptoms in many cases of acrodynia. The patients keep their eyes closed or protect them from light with their hands or arms. They turn away from light or burrow with their heads into the pillows. The conjunctivas are injected.

Coryza with discharge of nasal secretion is often seen in acrodynia. Some authors emphasized the continuous nasal secretion,[59] while most observers considered coryza as a complication rather than a symptom of acrodynia.

Nasopharyngitis and bronchitis are stressed by some authors and even considered causes of the disease.[60] In general, however, little attention was paid to the inflammatory manifestations of the upper respiratory tract, which were attributed to secondary bacterial invasion of organs which had lost their normal resistance.

Conjunctivitis, photophobia and lacrimation have been described in acute reactions to mercury, as well as in chronic mercury poisoning. Lewin [17] mentioned photophobia associated with mercurial dermatoses following internal administration of mercurial preparations. Engelmann [43] observed itching of the eyes and photophobia in a hypersensitive adult two hours after ingestion of small amounts of mild mercurous chloride. A patient of Bossard [24b] displayed a rash, photophobia and lacrimation four days after moderate amounts of mild mercurous chloride were given by mouth. A dental assistant who worked with amalgam fillings reacted to mercury with a dermatosis, photophobia and lacrimation.[37b] Conjunctivitis was one of the symptoms found by Neal and his associates [39b] in many workers with chronic mercurialism. In addition to conjunctivitis Almkvist [25] discussed mercurial enanthem, nonulcerative stomatitis, rhinitis, pharyngitis, bronchitis, laryngitis, urethritis, endometritis and vaginitis. It appears, therefore, that some of the catarrhal symptoms occurring in acrodynia could be explained as mercurial reactions rather than as secondary infections of the debilitated organism.

Intestinal Manifestations: Anorexia is an outstanding symptom of acrodynia, leading to loss of weight and emaciation. Vomiting is rare, but it was observed in a number of cases at the onset of the disease. In many descriptions of acrodynia constipation is stressed as an intestinal symptom. Feer [40] and Deuber [29b] described frequent, small and formed stools as characteristic of the disease. However, there are many cases of acrodynia on record in which diarrhea was an outstanding symptom. Bilderback [1] stated that " . . . the stools are frequently loose and foul smelling. Prolapse of the rectum is common." In the majority of cases observed by Deuber [29b] diarrhea persisting for weeks or months was the rule. Tenesmus

59. (*a*) Deuber.[29b] (*b*) Feer, E.: Eine eigenartige Neurose des vegetativen Systems beim Kleinkinde, Ergebn. d. inn. Med. u. Kinderh. **24**:100, 1923.

60. Rodda, F. C.: Acrodynia: A Clinical Study of 17 Cases, Am. J. Dis. Child. **30**:224 (Aug.) 1925.

and prolapse of the anus occurred frequently even in those patients who had formed but frequent stools. Tenesmus was often associated with attacks of abdominal pain or with severe attacks of perspiration and subsided together with these symptoms. Selter [54] confirmed these findings and described frequent soft or liquid stools in some of his patients and small spherical and frequent stools (spastic stools) in others. He stressed involvement of the rectum, evacuation of mucous or bloody masses with tenesmus and prolapse. The anal mucosa is described as loose and bluish red and the perianal area as macerated and fissured. Prolapse of the anus was observed by many authors.[61] Lorenz [61e] described ulceration of the rectal mucosa. Abdominal pain, though not stressed in many general descriptions of acrodynia, seems to be an outstanding symptom in numerous cases. Children complain for many days of abdominal pain, which may be present without intestinal disturbance or tenderness on pressure. Feer,[40] as well as Selter,[54] spoke of "navel colic," and other observers reported painful crises which come on suddenly, disappear rapidly or shift to other areas.[62] Levesque [63] stressed abdominal pain as an acrodynic symptom and spoke of a *forme douloureuse abdominale*. He compared the attacks of abdominal pain to tabetic crises.

In chronic mercury poisoning and in mercurial polyneuritis digestive disturbances and anorexia are common.[64] Constipation or diarrhea with tenesmus and violent abdominal pain were described as side effects of treatment by mercurial inunction.[17] Diarrhea, numerous stools with or without blood, tenesmus and abdominal pain may follow administration of mild mercurous chloride if the drug remains too long in the body.[17] Subacute mercury poisoning may take a gastrointestinal form, with colic and diarrhea, less often constipation. The colicky pains may be severe, and the discharges may be bloody.[37b] A physician who was obliged to give mercurial rubbings did so with his bare hands. He had three violent attacks of abdominal pain closely resembling lead colic.[37b] Intestinal disturbances and

61. (*a*) Keller.[31] (*b*) Bastible, M. S.: Two Cases of "Pink Disease," Irish J. M. Sc., May 1939, p. 220. (*c*) Chabrun, J., and Hollier, R.: Acrodynie infantile sévère avec mutilations digitales: Chute des dents et prolapsus rectal, Bull. Soc. pédiat. de Paris **33**:202, 1935. (*d*) Mouriquand, G.; Lamy; Weill, and Savoye, J.: Trois cas de proplapsus rectal dans l'acrodynie, Lyon méd. **155**:373 1935. (*e*) Lorenz, E.: Zum Wesen und zur Behandlung der Feerschen Krankheit, Arch. f. Kinderh. **111**:65, 1937. (*f*) Wolf, I. J., and Davison, C.: Acrodynia (Erythredema, Polyneuritis, Vegetative Neurosis, Pink or Swift Disease): A Histopathologic Study of the Nervous System, J. Pediat. **4**:498, 1934.

62. (*a*) Mayerhofer.[2c] (*b*) Deuber.[29b] (*c*) Zechlin.[55c] (*d*) Blackfan, K. D., and McKhann, C. F.: Acrodynia: A Note on the Pathologic Physiology, J. Pediat. **3**:45, 1933. (*e*) Janet, H., and Pierrot, R.: Un cas d'acrodynie chez un enfant de 7 ans avec symptômes passagers d'encéphalite, Bull. Soc. pédiat. de Paris **24**:422, 1926. (*f*) Levesque, J., and Méry, R.: Acrodynie probable caractérisée par un syndrome abdominal douloureux, ibid. **31**:528, 1933. (*g*) Müller, H.: Ein Beiträg zur Neurose des vegetativen Systems beim Kleinkinde (Feer), Arch. f. Kinderh. **81**:81, 1927. (*h*) Porter, L.: Dermatopolyneuritis (Thursfield, Patterson), Acrodynia (Weston), Erythredema (Swift), M. Clin. North America **6**:431, 1922.

63. Levesque and Méry.[62f] Levesque, J.: Sur une forme atypique de l'acrodynie: La forme douloureuse abdominale; Considérations sur le traitement de l'acrodynie, Rev. de méd., Paris **55**:196, 1938.

64. (*a*) Spillmann and Étienne.[32] (*b*) Neal and others.[39b] (*c*) Leyden, E.: Ueber Polyneuritis mercurialis, Deutsche med. Wchnschr. **19**:733, 1893.

diarrhea occur in mercurial polyneuritis.[65] A patient of Colin and Dutil [66] suffered from violent colic without diarrhea following mercurial injections. Bossard [24b] observed in an adult who had received in three days a total of 1.5 Gm. of mild mercurous chloride ulcerative stomatitis, ulceration of the anal mucous membrane and necrosis of the perianal skin.

Gangrenous and Necrotic Manifestations: Gangrene and necrosis of the skin, of the phalanges, of the nose and of the external ear have been observed in many cases of acrodynia. The subject was thoroughly discussed by Gadrat, Lasserre and Petel,[67] who reviewed the French literature on this subject. Mutilation of the hands, feet or face is the end result in those children who survive such severe forms of acrodynia. Almkvist [25] studied necrotic changes of the mucous membranes in mercury intoxication. He concluded that mercury forms mercury sulfide in the endothelial cells of capillaries when it combines with hydrogen sulfide. The hydrogen sulfide is formed by bacterial protein decomposition. Gangrene of the fingers following mercury medication was described by Gwalter in 1877.[36] The case was described as one of "pemphigus mercurialis," but it shows sufficient resemblance to acrodynia to deserve citation here:

> A child of nonsyphilitic parents exhibited a pustular rash. At the order of a "quack" inunctions of mercuric oxide were applied in various places for t[h]ree weeks. An enormous stomatitis developed, whereby the teeth fell out. A physician ordered gargling with potassium chlorate solution, and the stomatitis healed within a short time. However, two months after the mercury treatment mentioned above new signs of intoxication appeared. On various places of the body large white vesicles formed which soon became black and discharged putrid pus; the surroundings of the vesicles were gangrenous. There was again stomatitis ulcerosa present; gangrene of the three middle fingers of the left hand set in. On both hands there was at the level of the metacarpophalangeal joints a large, deep loss of substance with fetid suppuration. The feet were swollen, and on the left there was an ulcer of the size of a *Fünf-Rappenstück*. Bloody stools developed and accelerated the death of the child.

The literature on acrodynia also reports the occurrence of necrotic phenomena in a few children who had received mercury treatment before the onset of the disease. In Verboom's patient [68] gangrene of hands and feet and necrosis of the oral mucous membranes occurred after a worm treatment with santonin and mild mercurous chloride. Zahorsky's patient,[29c] who had received "tablets" because of ascariasis, had ulcers on a finger as well as in the mouth. In Keller's case 2,[31] in which there developed acrodynia "after ascaris worms were passed," the disease "terminated in a typical Raynaud's gangrene with loss of the terminal finger links." In Weber's case [69] the diagnosis of acrodynia is not generally accepted and the sequence of events not entirely clear. The child had apparently some symptoms as early as 3 weeks of age. At one time a diagnosis of syphilis was considered. In

---

65. Spillmann and Étienne.[82] Adler.[52]

66. Colin and Dutil: Un cas d'ophtalmie sympathique grave, suivi à la fin du traitement d'un syndrome spinal singulier (algies et contractions fibrillaires violentes) et terminé après quelques semaines de durée par guérison complète, Rev. d'oto-neuro-opht. **10**:425, 1932.

67. Gadrat, J.; Lasserre, J., and Petel, R.: Sur les mutilations digitales dans l'acrodynie infantile. Arch. de méd. d. enf. **42**:559, 1939.

68. Verboom, C. H.: Acrodynia with Gangrene of Hands and Feet, Nederl. tijdschr. v. geneesk. **83**:1362, 1939.

69. Weber, F. P.: Case of Erythroedema (the "Pink Disease") and the Question of Acrodynia (Epidemic Erythema), Brit. J. Child. Dis. **19**:17, 1922.

the course of the disease a thorough trial was made of mercurial preparations, of an ammoniated mercury ointment for the hands and feet and of mercury bichloride solution (1:1,000) for painting the nasal passages once daily. When the child was demonstrated at the age of 2½ years,

> . . . the condition, in regard to the hands and feet, might almost have been termed "acrodermatitis chronica mutilans." There was extreme redness of the cheeks and chin, and the skin of the cheeks was slightly scaly. There was a chronic offensive mucopurulent discharge from the nose, the bridge of which was very depressed. The skin of the hands tended usually to be swollen and red or cyanotic. The tips of some of the fingers had been lost by gangrene or ulceration. The feet, like the hands, tended to be turgid and red or livid, and in each sole there was an irregularly shaped chronic ulcer. . . .

Manifestations in the Nervous System: Children suffering from acrodynia lose their good disposition, become irritable and hostile to their surroundings. They sigh and complain and present a picture of depression. They hide the face, bite their fingers and may fly into sudden rages. Delirum and hallucinations occur in older children. There may be complete confusion, loss of speech and anxiety states. Insomnia is an outstanding symptom in most cases of acrodynia. Children at first appear restless and excitable and throw themselves about. Later they may remain awake for days or weeks unable to find rest. Attacks of pain, itching and general discomfort contribute to the insomnia. Somnolence and drowsiness occur in exceptional cases.

Motility is always impaired. In mild cases movements are reduced because of listlessness or pain, or the motions may be slow and uncoordinated. Older children who can walk have a waddling gait similar to that of patients with muscular dystrophy.[40] They walk for short distances only, looking for support as soon as possible. Most children with acrodynia are too weak to walk. They lie in bed in bizarre positions which are made possible by the flaccidity of their muscles. There is marked hypotonia, and passive movements find little resistance, although some movements can usually be elicited by pinprick. The tendon reflexes are decreased in the majority of patients, but increased reflexes have also been observed.[70] True motor paralysis is rare but has occurred in a number of patients.[71] Some authors have considered the neurological complications of acrodynia to be due to a polyneuritis[72]; others speak of myelitis.[73] Encephalitic symptoms were prominent in

70. Byfield.[6] Feer.[40]

71. (*a*) Blackfan and McKhann.[62d] (*b*) Van Bogaert, L.; Koumans, V., and Sweerts, J.: Sur l'acrodynie de l'enfant et de l'adulte, Rev. franç de pédiat. **4**:86, 1928. (*c*) Schwartz, A. B.: Dermatopolyneuritis with Motor Paralysis of the Lower Extremities, Am. J. Dis. Child. **39**:359 (Feb.) 1930. (*d*) Debré, R.; Marie, J., and Messimy: Forme quadriplégique de l'acrodynie, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1075, 1934. (*e*) Marie, J.: L'acrodynie paralytique grave avec dissociation albuminocytologique de liquide rachidien, Arch. franç. pédiat. **1**:217, 1943.

72. Byfield.[6] Thursfield, H., and Paterson, D. H.: Dermato-Polyneuritis (Acrodynia; Erythroedema), Brit. J. Child. Dis. **19**:27, 1922. Paterson, D., and Greenfield, J. G.: Erythroedema Polyneuritis: So-Called Pink Disease, Quart. J. Med. **17**:6, 1923. Foerster, H. R.: Erythredema Polyneuritis, Arch. Dermat. & Syph. **12**:17 (July) 1925. Younkman, J. H.: Erythredema Polyneuritis (Pink Disease), M. J. Australia **1**:473, 1934.

73. (*a*) Orton, S. T., and Bender, L.: Lesions in the Lateral Horns of the Spinal Cord in Acrodynia, Pellagra, and Pernicious Anemia, Bull. Neurol. Inst. New York **1**:506, 1931. (*b*) Mayerhofer, E.: Atypische Poliomyelitiden und deren ätiologische Beziehung zur infantilen Akrodynie, Ann. pædiat. **153**:144, 1939. (*c*) Delmas-Marsalet, P.: Les myélites acrodyniques, J. de méd. de Bordeaux **123**:24, 1946.

some patients.[74] In recent years cases have been described which assume the picture of the Landry-Guillain-Barré syndrome.[75] It has been known for some time that a number of patients with acrodynia may show increased total protein values in the spinal fluid without increase in cells.[1] At present observers wonder whether or not a sharp differentiation can be made between acrodynia with symmetrical flaccid paralysis and the Guillian-Barré syndrome with acrodynic manifestations.[76]

Tremor is frequently present in acrodynia and often so fine that it is overlooked. Sometimes, however, it is coarse and obvious. Arms and hands are chiefly affected, the tremor becoming noticeable in intentional movements.[77] Muscular twitching, grimacing and choreomyoclonic movements occur. Convulsions have been described in many cases.[78] They may initiate the disease and precede other symptoms of acrodynia by several weeks. They may be followed by somnolence and transitory paralysis.[54]

A diminution in cutaneous sensibility was demonstrated in some of the cases, but evaluation of the findings is usually difficult in infants and small children who do not cooperate. Paresthesias are described frequently in the history of older children. Numbness, formication, burning, itching and pain torment the patients. Some children are taken suddenly by paroxysms of crises of pain.[79] Eschbach [29e] spoke of lancinating pain. These attacks may befall a child during his play and

---

74. (*a*) Janet and Pierrot.[62e] (*b*) Rocaz: Acrodynie infantile avec encéphalo-myélite terminale, Bull. Soc. pédiat. de Paris **27**:482, 1929. (*c*) Thomas, A.: Acrodynie ou névraxite, Médecine **19**:106, 1938. (*d*) Bourrée, J.: L'acrodynie infantile: Ses aspects encéphalitique, Paris, 1938; cited by Guillain, G., and Tiffeneau, R.: Form acrodynique infantile du syndrome de polyradiculonévrite, Bull. Acad. de méd. **124**:527, 1941; cited by Marie.[71e] (*e*) Dijkstra, B.: Infantile Acrodynia and Encephalitis, Maandschr. v. kindergeneesk. **9**:292, 1940. (*f*) Lapage, C. P.: Encephalomyelitis in a Case of Pink Disease, Brit. M. J. **2**:728, 1941. (*g*) Chaptal, J.; Guibert, H. L., and Sarran, R.: Acrodynie: Encéphalite terminale, Montpellier méd. **21-22**:485, 1942.

75. (*a*) Footnote 71 *b* and *e*. (*b*) Rocaz.[74b] (*c*) Péhu, M., and Boucomont, J.: L'acrodynie infantile, Paris, Masson et Cie, 1944. (*d*) Glanzmann, E., cited by Fanconi [76c]; (*e*) Paralytische Form der Akrodynie mit Dissociation albumino-cytologique des Liquor cerebrospinalis (Guillain-Barré Syndrome), Ann. pædiat. **167**:353, 1946. (*f*) Janet, H.; Odier-Dollfus, and Lesca, H.: Syndrome de Guillain-Barré avec signes encéphalitique, cardiovasculaires et acrodyniques passagers, Bull. Soc. pédiat. de Paris **38**:431, 1941. (*g*) Guillain, G., and Tiffeneau, R.: Bull. Acad. de méd. **124**:527, 1941; cited by Marie.[71e]

76. (*a*) Marie.[71e] (*b*) Guillain and Tiffeneau.[75g] (*c*) Fanconi, G.; Zellweger, H., and Botsztejn, A.: Die Polyradiculitis und ihre Differentialdiagnose, Ann. pædiat. **162**:59, 1944. (*d*) Zellweger, H., in discussion on Glanzmann.[75e]

77. (*a*) Footnote 29 *b* and *d*. (*b*) Keller.[31] (*c*) Feer.[40] (*d*) Doig.[47] (*e*) Zechlin.[55c] (*f*) Footnote 62 *d* and *g*. (*g*) Schwartz.[71c] (*h*) Jäger, O.: Ein Fall von vegetativer Neurose Feer beim Kleinkinde (Akrodynie), Ztschr. f. Kinderh. **39**:239, 1925. (*i*) Emerson, P. W.: Case of Acrodynia, J. A. M. A. **77**:285 (July 23) 1921. (*j*) Dragišić, B.: Annuläre Hautblutungen bei einem Falle von infantiler Akrodynie (Feer), Ztschr. f. Kinderh. **55**:721, 1933. (*k*) Lévy, P. P., and Schneider, J.. Syndrome acropathologique avec troubles du caractère, tremblement et aréflexie, tachycardie: Evolution très lentement régressive; Etiologie indéterminée à rapprocher à certains égards de l'acrodynie, Bull. Soc. pédiat. de Paris **34**:540, 1936.

78. (*a*) Footnote 29 *b* and *c*. (*b*) Selter.[54] (*c*) Lorenz.[61e] (*d*) Blackfan and McKhann.[62d] (*e*) Caussade, L.; Watrin, J., and Neimann, N.: L'acrodynie maligne, Arch. de méd. d. enf. **42**:91, 1939. (*f*) Sweet, G. B.: Acrodynia, Arch. Pediat. **42**:543, 1925. (*g*) Péhu, M.; Dechaume, J., and Boucomont, J.: Sur l'acrodynie infantile: Anatomie pathologique de l'acrodynie infantile, Rev. franç. de pédiat. **12**:239, 1936.

79. Footnote 29 *a* and *b*. Janet and Pierrot.[62e] Péhu and others.[78g]

make him cry out suddenly in extreme pain. Older children show these paroxysms oftener than infants. The hands, feet, joints, arms, legs and back may be the site of such painful sensations, causing sleeplessness in many cases.

Psychical changes in patients with chronic mercury poisoning are well known. Many descriptions are derived from observation of cases of industrial mercury intoxication. The symptoms vary somewhat, since there are differences in the manner of exposure as well as in the quantity of mercury absorbed. Persons vary widely in degree of susceptibility. Some workers display symptoms soon after entering the factory, others many years later, and some remain resistant and symptom free. In spite of these differences the psychical changes of mercurial poisoning are described uniformly. Irritability, excitability, anxiety, timidity, unreasonableness, crankiness, depression, melancholy, suicidal tendencies, delirium and hallucinations have been observed.[80] A patient of Spillmann and Étienne [82] who had mercurial polyneuritis was described as having been depressed at first and paranoid later in the disease. Doig's patient [47] who had "pink disease" following mercurial inunction was depressed and presented a picture of extreme misery. Keller's patient [81] who acquired acrodynia following external application of mercury bichloride was apathetic, whiney, irritable and easily angered. Mayerhofer and Dragišić [53] reported the case of a boy who exhibited infantile acrodynia following several treatments for worms with mild mercurous chloride and santonin. He became "bad and unmanageable" and had nervous attacks combined with abdominal colic. During a relapse he showed character changes and melancholic depression.

Insomnia has been described in connection with mercurial intoxication by many authors. It is mentioned by Lewin [17] among the nervous symptoms. Hamilton,[37b] in discussing industrial mercury poisoning, stated: "Sometimes insomnia is the chief complaint, or bad dreams or depression and loss of memory." Adler [52] and Neal [39b] mentioned it as a symptom of patients with chronic industrial mercurialism. Insomnia is associated with mercurial dermatoses [81] and with mercurial polyneuritis.[82]

Impairment of motility resembling that of acrodynia occurs in many instances of mercury poisoning. In mercurial paralyses the muscles are flaccid but usually not atrophic.[64c] Patients with mercurial polyneuritis show muscular weakness or paralysis, unsteady gait or inability to stand, ataxia and sometimes muscular atrophy. The tendon reflexes may be decreased or increased.[83] Recovery follows in most of these cases after several weeks or months. However, Brauer's patient,[84] who had bulbar symptoms in addition to flaccid paralysis of the extremities, died several months after mercury treatment and onset of polyneuritic symptoms. Disturbance of bladder function occurred in the patients of Brauer [84] and Gilbert.[33a]

80. Stock.[27] Hamilton.[37b] Neal and others.[39b]

81. Bass.[22e] Engelmann.[43]

82 (*a*) Spillmann and Étienne.[82] (*b*) Adler.[52] (*c*) Leyden.[64c] (*d*) Spitzer, L.: Ein Beitrag zur Kenntniss der mercuriellen Polyneuritis acuta, Deutsche Ztschr. f. Nervenh. **19**:215, 1900-1901.

83. (*a*) Spillmann and Étienne.[82] (*b*) Footnote 33. (*c*) Leyden.[64c] (*d*) Spitzer.[82d] (*e*) Favorski, A.: Neurol. Centralbl. **19**:375, 1900; cited by Spitzer.[82d] (*f*) von Engel, R.: Ueber Polyneuritis mercurialis, Prag. med. Wchnschr. **19**:65 and 79, 1894.

84. Brauer, L.: Letal endende Polyneuritis bein einem mit Quecksilber behandelten Syphilitischen, Berl. klin. Wchnschr. **34**:267 and 294, 1897.

In two cases mercurial polyneuritis followed mercury bichloride poisoning after the acute symptoms had subsided. One patient [83e] recovered after six months, while the second [85] died presenting a typical picture of ascending Landry's paralysis (acute ascending myelitis). Landry-Guillain-Barré syndrome developed in a boy described by Fanconi and his co-workers [76c] following ingestion of mild mercurous chloride during a treatment for worms. Patient 27 in the present series showed symptoms of acrodynia following the use of diapers rinsed in mercury bichloride solution. His muscles became so flaccid that he could not stand, sit or support his head. He could not void spontaneously, was unable to cough or swallow and died in respiratory failure. The protein in the spinal fluid was greatly elevated. He represents an instance of acrodynia with Landry-Guillain-Barré syndrome of mercurial origin.

It has been pointed out that tremor is a frequent symptom of acrodynia, although its occurrence has not been stressed in general descriptions of the disease. This is unfortunate because emphasis on this symptom could have led to an earlier recognition of the mercurial origin of acrodynia. Tremor is an outstanding sign of subacute and chronic mercury poisoning. As early as the ninth and tenth centuries Arabian physicians knew that tremor, convulsions, muscular twitchings and cramps in the extremities were signs of mercury intoxication.[25] Ullrich von Hutton described the nervous changes during mercurial treatments as follows:

> In many the brain was infected to the point of vertigo in some even to the extent of insanity. Not only the hands trembled but even the feet and the whole body and the tongue contracted a stammering in some cases incurable.[56]

Paracelsus (1493-1549), who wrote a book on miner's sickness, devoted one third of his monograph to mercury. He emphasized tremor, putrefaction of the mouth (stomatitis), looseness and loss of teeth and strong stabbing pain [86] as signs of mercury poisoning. Tremor of industrial mercury poisoning is known as "miner's shakes" or "hatter's shakes." In the nineteenth century Kussmaul [87] described mercurial tremor in workers in mirror factories. In the early stages of intoxication mercurial tremors in fine, later small, chorea-like quivers appear, the gait becomes staggering and coordination is disturbed.[88] Tremor following mercurial medication was emphasized by Lewin.[17] The muscles become extremely weak without being paralyzed, in contrast to the true paralysis seen in lead poisoning. In mercurial polyneuritis tremor may be associated with muscular twitching.[65] Doig's patient [47] who exhibited acrodynia after use of a mercurial ointment had a coarse tremor in the lower limbs sufficient to cause twitching of the toes.

Disturbance of sensibility, anesthesia and hyperesthesia have been described in mercury intoxication.[89] In mercurial polyneuritis sensibility is usually disturbed; paresthesias,[64c] numbness of the hands and feet,[90] formication [91] and burning sen-

85. Kétli, cited by Leyden.[64c]

86. Paracelsus, cited by Rosen, G.: The History of Miners' Diseases: A Medical and Social Interpretation, New York, Schuman's, 1943.

87. Kussmaul, A.: Untersuchungen über den constitutionellen Mercurialismus und sein Verhältniss zur constitutionellen Syphilis, Würzburg, Stahel, 1861.

88. Leschke.[18b] Hamilton.[27b]

89. Lewin.[17] Leyden.[64c]

90. Leyden.[64c] Brauer.[84]

91. Spillmann and Étienne.[82] Forestier.[33b]

sations at the tip of the fingers and of the tongue [32] have been described. Pain is an outstanding symptom. The pains are described as lancinating,[92] intense, dull and atrocious [93]; patients cry and howl when the attacks come on [94] and cannot find rest [32] or sleep for many days and nights.[82d] Doig's patient,[47] mentioned above, had burning pain in the feet and hands which was resistant to use of sedatives and kept him awake. He also had pains in the legs and back, especially in the lumbar region, and in the region of the shoulder girdle.

Hemorrhagic Manifestations: Annular cutaneous hemorrhages were described in infantile acrodynia by Dragišić,[77j] and purpuric manifestations on the hands [75g] and on the toes [53] were reported. Palpebral, subconjunctival and orbital hemorrhages occur.[29b, d] Bleeding from mouth and nose [29b] and from the bowels [95] has been observed. Acrodynia terminated by a fatal hemorrhage was reported by Reed.[96]

Purpuric manifestations on the skin following mercurial inunctions were mentioned by Bossard [24b] and Lewin.[17] In a fatal case of mercury intoxication following injections of mild mercurous chloride,[97] nosebleeds and dysenteric symptoms were described. In chronic mercurialism punctate hemorrhages under the skin, nosebleeds and intestinal bleeding were observed.[37b]

Tachycardia and Hypertension: These symptoms have been stressed by Feer [59b] as cardinal symptoms of acrodynia, an opinion not entirely shared by Selter.[54] Hypertension may be absent in mild cases and in cases of long standing.

Tachycardia in mercurialism was mentioned by Lewin.[17] The patients of Morvan [98] and Porot [99] who showed fibrillary chorea following mercurial medication and Doig's patient [47] who manifested "pink disease" after mercurial inunctions had tachycardia. No statements are available in the older literature on mercurialism concerning blood pressure. It is sometimes stated that the blood pressure is low in chronic mercurialism, but abnormally high blood pressure has also been observed.[37b]

Hyperglycemia and Glycosuria: Hyperglycemia in acrodynic children was observed by Feer,[40] Sommer,[100] Van Bogaert,[71b] Blackfan [62d] and Mayerhofer [73b] and particularly emphasized by Glanzmann.[75d] Dextrose tolerance curves comparable to those of diabetes were repeatedly reported.[101] Glycosuria is not rare.[102]

---

92. Spillmann and Étienne.[82] Leyden.[64c]

93. Spillmann and Étienne.[82] Leyden.[64c] Spitzer.[82d]

94. Spillmann and Étienne.[82] Spitzer.[82d]

95. Selter.[54] McDonald, S. F.: Swift's or Pink Disease: Recent Work on Pathology and Treatment, M. J. Australia **2**:276, 1933. de Lange, C.: Zur mikroskopischen Anatomie des Zentralnervensystems bei Pink Disease (Akrodynie, vegetative Neurose des Kleinkindes [Feer]), Jahrb. f. Kinderh. **136**:193, 1932.

96. Reed, J. S.: Pink Disease with Fatal Hemorrhage, M. J. Australia **2**:52, 1936.

97. Runeberg, J. W.: Quecksilberintoxication mit tödtlichem Ausgang nach subcutanen Calomelinjectionen, Deutsche med. Wchnschr. **15**:4, 1889.

98. Morvan: De la chorée fibrillaire, Gaz. hebd. de méd. **27**:173, 186 and 200, 1890.

99. Porot, A.: Un cas ancien, mais inédit de chorée fibrillaire de Morvan, Rev. neurol. **1**:581, 1934.

100. Sommer, K.: Neuer Beitrag zur Feerschen Krankheit (klindliche Akrodynie) (klinische und pathol. - anatomische Beobachtungen an 21 Fällen), Arch. f. Kinderh. **115**:232, 1938.

101. Feer.[40] Blackfan and McKhann.[62d] Mayerhofer.[73b] Glanzmann.[75d]

102. Bilderback.[1] Feer.[40] Woringer.[55b] Blackfan and McKhann.[62d] Eschbach, H.: Acrodynies infantiles, Bull. Soc. pédiat. de Paris **35**:60, 1937.

Hyperglycemia and glycosuria have been reported in cases of chronic mercurialism [37b] and studied experimentally in animals with mercury poisoning. Lewin [17] mentioned experimentally produced diabetes, and Almkvist [25] spoke of "diabetes mercurialis" in dogs, cats and rabbits.

Albuminuria: Traces and small amounts of albumin are often found in the urine of children with acrodynia.[103] There is nothing characteristic about the albuminuria, and the symptom has been given little attention.

Albuminuria is detected frequently in persons with chronic mercurialism.[37b] Albumin in the urine is not rarely observed after external or internal mercurial medication.[17] Albuminuria was observed in mercurial polyneuritis [104] and in fibrillary chorea [98] following mercurial inunctions.

In the foregoing pages we have attempted to show that the symptomatology of acrodynia and that of mercurialism overlap in many respects. The oral changes seen in cases of severe acrodynia, such as loosening and loss of teeth, gangrene of the mucous membranes and necrosis of the jawbones, are so characteristic of mercury poisoning that one wonders that they did not betray the mercurial origin of acrodynia long ago. Tremor, an outstanding symptom of mercurialism, was not

TABLE 3.—*Source of Mercury in Twenty-Three Cases of Acrodynia*

	Number of Children
Calomel-containing "teething powders"	11
Calomel-santonin for worm treatment	3
Calomel	3
Ammoniated mercury ointment	2
Mercury bichloride as diaper rinse	4
Total	23

sufficiently stressed by the students of acrodynia, although it is frequently present. Hypertension, on the other hand, though considered characteristic of acrodynia, is not a recognized symptom of mercurialism. We do not wish to imply that acrodynia and mercurialism are identical conditions. It will be pointed out later that mercurialism has various manifestations, one of which is acrodynia.

Possible Sources of Mercury.—In 38 of the 41 acrodynic patients of our series mercury was found in the urine. In 23 of these the source could be ascertained by questioning the parents. Table 3 shows that calomel-containing teething powders accounted for most of the cases of known exposure. Worm pills, mild mercurous chloride, ammoniated mercury ointment and diaper rinses of mercury bichloride accounted for the rest. Not all parents could be questioned properly about their children's exposure to mercury. In some of the cases the correct information was not obtained without special questioning, since the parents were unaware that mercurial preparations had been given. There must be other sources in addition to those mentioned above, since exposure to mercury was demonstrated in some of the patients by finding the metal in the urine, although mercurial medication was denied. It must be remembered that mild mercurous chloride was and probably still is used freely in many forms and for a treatment of a variety of diseases of

103. Woringer.[55b] Blackfan and McKhann.[62d]

104. Spillmann and Étienne.[82] von Engel.[83f]

children. In the past treatment of any febrile disorder was usually begun by catharsis with mild mercurous chloride followed by castor oil or a saline laxative.[105] In the treatment of ascariasis and oxyuriasis administration of santonin and mild mercurous chloride was a standard procedure which still is followed in many parts of the world. In areas of endemic ascariasis "worm chocolate" or "worm candy" containing mild mercurous chloride can be bought at the drug stores without prescription [106] and is given for worms or other abdominal disorders by the mother, usually not followed up by another laxative. We do not know when or where the custom of "teething powders" originated, what the rationale for their administration was or why mild mercurous chloride was included in their composition. It seems that mercury-containing teething powders were an old household remedy in England. Dr. Harold N. Cole, of Cleveland, Ohio, directed our attention to an article written by Jonathan Hutchinson [107] in 1875 in which he stated:

> There seems reason to believe that in a large number of cases in which infants suffer from fits, mercury is given, and not infrequently in large and repeated doses. I believe that it also enters into the composition of the most popular teething powders.

It was also known to Hutchinson that stomatitis, an outstanding symptom of the severe form of acrodynia, may follow administration of mercury-containing teething powders (p. 354). Teething powders containing mild mercurous chloride are still used in England,[108] Australia,[109] Canada and in the South in the United States. All our 11 patients who had acrodynia following the administration of teething powders lived in southern states. Dr. Vera Buhrman, of Pretoria, South Africa, supplied us with three popular teething powders used in South Africa, and it was found that all of them contained mercury. In all these areas acrodynia is a relatively frequent disease. Mercury bichloride is used for disinfecting diapers, dressings, washes, baths, in eye drops and ointments. Ammoniated mercury ointment is employed in the treatment of impetigo, psoriasis, eczema, intertrigo, pediculosis pubis, etc. Yellow mercuric oxide ointment may be employed for application to the eye and in treatment of pediculosis and skin infection. Mercury has been given by inunction against syphilis since the end of the fifteenth century. Mercurial medicaments have been replaced by other drugs for many of the purposes mentioned, but they reappeared in the form of new compounds and for different uses. Mercurial preparations are now generally used as skin disinfectants and considered as harmless, but it is very likely that one can become sensitized by them after repeated applications.[110] Mercurial diuretics are of great benefit in the treatment of cardiac insufficiency, but even in their modern forms they are not completely innocuous. Severe forms of mercurial stomatitis, mercurial angina and dermatitis ulcerosa were observed following administration of mersalyl (salyrgan®) and Esidron (sodium salt of pyridenedicarboxyl-β-mercurin-γ-hydroxypropylamide and theophylline) in customary doses.[35]

---

105. Rachford, B. K.: Diseases of Children, New York, D. Appleton & Co., 1912.

106. (*a*) Fanconi and others.[28] (*b*) McKenzie, A. F.: Acrodynia? Canad. M. A. J. **13**:43, 1923.

107. Hutchinson, J.: Imperfect Teeth and Zonular Cataract, Brit. M. J. **1**:307, 1875.

108. Mercury and Pink Disease, Annotations, Lancet **1**:838, 1948.

109. Clayton-Jones, E.: Personal communication to the authors, June 1948.

110. Baumann.[28] Underwood, G. B.; Gaul, L. E.; Collins, E., and Mosby, M.: Overtreatment Dermatitis of Feet, J. A. M. A. **130**:249 (Feb. 2) 1946.

While in many of our cases of acrodynia medication was the source of mercury, accidental exposure to mercury is possible and may account for the presence of the metal in the body and urine and for adverse reactions. Small amounts present in industrial products may cause reactions in sensitive persons. Mercurial compounds are employed in the manufacture of fireworks and "Pharaoh's serpents," which contain mercuric sulfocyanate, and have been responsible for serious mercurial reactions.[111] Amalgam dental fillings, particularly those made of copper amalgam, have elicited signs of mercury intoxication.[112] Ammoniated mercury is used in many cosmetic preparations, such as freckle removers and skin bleaches.[24c] Mercuric sulfide is found in red sealing wax. Mercury bichloride is a wood preservative and one of the chemicals employed against termites. Phenyl mercury compounds are powerful insecticides and fungicides used in mildew-proofing of fabrics. They are also skin irritants and may cause dermatitis in sensitive persons wearing fabrics (shoes) impregnated with such mercurial compounds. Methyl mercury compounds and other organic mercury compounds prevent smut diseases of cereals. Such compounds are employed as seed dressings for wheat, barley and oats.[113] Mercuric nitrate was employed in the carroting of rabbit fur in the preparation of felt hats.[114] A finished felt hat may contain 0.85 per cent of mercury.[115] Mercury was employed in the past in the fabrication of mirrors, and old mirrors still contain mercurial compounds. Mercury is used in the manufacture of batteries and pocket dry cells. Small children who play with household articles and have an opportunity to chew them may be exposed to mercury from unexpected sources, and it is possible, therefore, that the metal may be found in the urine without preceding medication.

Mercury and the Older Literature on Acrodynia.—We reviewed a limited number of case reports published on acrodynia in the last three decades in order to ascertain whether mercurial medication preceding the outbreak of the disease was recorded in any of them. Since none of the authors, with the exception of Zahorsky,[58] considered mercury as a possible etiological factor in acrodynia, we had to search for more or less casual statements in the patients' past histories and had to rely in some of the cases on circumstantial evidence. Many reports do not give a satisfactory past history, and others mention a preceding disease but fail to indicate the medicament administered. This is regrettable, since some patients had impetigo, dermatitis, eczema, diaper rashes, constipation, diarrhea or enteritis before onset of acrodynia, conditions which were treated frequently at the time with mercurial preparations. In the absence of definite statements concerning medication such case reports did not contribute much to the question of the causation of acrodynia. In English reports one finds rather often the statement that the child was well until teething began. Based on recent findings,[116] one may suspect that teething powders

111. Engelmann.[43] Cave, F. E.: Poisoning by Mercuric Sulpho-Cyanide, Brit. M. J. **2**:873, 1885.

112. Bass.[22e] Stock.[27]

113. Hunter, D.; Bomford, R. R., and Russell, D. S.: Poisoning by Methyl Mercury Compounds, Quart. J. Med. **9**:193, 1940.

114. Schwartz and others.[24c] Neal and others.[39b]

115. Minot, A. S.: Estimations of Mercury in Hatters' Fur and in Felt, J. Indust. Hyg. **4**:253, 1922.

116. (*a*) Warkany and Hubbard.[15] (*b*) Footnote 108. (*c*) Bivings, L., and Lewis, G.: Acrodynia: A Treatment with BAL, J. Pediat. **32**:63, 1948. (*d*) Bivings, L.: Acrodynia: A Summary of BAL Therapy Reports and a Case Report of Calomel Disease, ibid. **34**:322, 1949.

containing mild mercurous chloride were the source of mercury in such children, but it is not possible to prove this point at this late date. It will be useful, however, in the future to ask mothers who date the outbreak of acrodynia from the time of "teething" whether they gave the child teething powders or not. The search was more successful in regard to statements concerning ascariasis and vermifuges. Evacuation of ascarides is mentioned in the cases of Feer,[59b] case 3; Keller,[31] case 2; Jenny[19]; Janet and Pierrot[62e]; Janet and Huguet.[117] Ascariasis and worm treatment were described in the reports of Selter[54]; Müller,[62g] case 4: worm chocolate, two treatments; McKenzie,[106b] case 1: worm medicine; case 2: worm medicine and worm powders; Ihm,[118] worm treatment. A patient of Zahorsky[29c] had suffered from a worm infection (Ascaris) for which some tablets were given, and three worms were passed. Several months later she had abdominal pain and vomiting and became irritable. She was given more worm medicine and evacuated more worms. Then a rash appeared, and other typical acrodynic symptoms followed. Verboom's patient[68] had acrodynia with gangrene of the hands and feet, loss of teeth and necrosis of oral mucous membranes after "santonin treatment" for ascaris. A patient of Mayerhofer and Dragišić[53] had abdominal colic. Ascaris, Oxyuris and Trichocephalus dispar (Trichuris trichiura) ova were found in the stools, and several worm treatments with mild mercurous chloride and santonin were given. The authors wrote that the condition did not improve. The child even had a peculiar exanthem with peeling palms and soles (attack of acrodynic desquamation with accompanying rash) which then was erroneously considered a possible calomel intoxication. A patient of Fanconi, Zellweger and Botsztejn[76c] displayed Landry-Guillain-Barré syndrome after two worm treatments with santonin and mild mercurous chloride (compare with cases 27 and 33 of our series; see also p. 358). Several acrodynic patients of Zahorsky[58] had been given mild mercurous chloride before the onset of the disease. Currie's patient[45] received mild mercurous chloride before the outbreak of a "subacute" case of acrodynia (see p. 351). The patient of Poinso, Brunel and Morel[119] had anorexia, irritability, disturbance of gait and pyodermia. Since some relatives had syphilis he was treated with mild mercurous chloride and acetarsone (stovarsol®). Two weeks later he had typical acrodynia with nephritis. Doig's patient[47] was treated with a mercurial ointment for pediculosis pubis before he showed acrodynia. Keller's patient (case 1[31]) had a localized rash on the buttocks and face which was treated with mercury bichloride washes and ointment. Two weeks later she exhibited atypical "measles" and two months later acrodynia. In Weber's patient[69] a thorough trial of mercurial treatment had been made; ammoniated mercury ointment was used for the hands and feet, and the nasal passages were painted daily with mercury bichloride solution (see p. 357).

These examples show that in a number of cases of acrodynia reported in the older literature administration of mercurial preparations is mentioned, although no connection between the medication and acrodynia was considered. In two

117. Janet, H., and Huguet, S.: Un cas d'acrodynie chez une enfant de 3 ans et demi: Précocite et longue durée des troubles oculaires, Bull. Soc. pédiat. de Paris **30**:476, 1932.

118. Ihm, L.: Beitrag zur Kenntnis der Feerschen Neurose des vegetativen Systems beim Kleinkinde, Klin. Wchnschr. **4**:2351, 1925.

119. Poinso, R.; Brunel, J., and Morel, R.: Deux nouveaux cas d'acrodynie infantile en Provence, Marseille méd. **1**:441, 1935.

instances [120] the possibility of a causal connection between administration of mild mercurous chloride and acrodynia was considered and rejected. In some reports the time relationship between worm treatment and outbreak of acrodynic symptoms is not clear. Abdominal pain, irritability or a rash may precede the administration of the mercurial preparation, and it may appear doubtful that the medication elicited the disease. However, in several cases [121] the symptoms were indefinite before and typical after the ingestion of the mild mercurous chloride. In a similar case (case 2 [106b]) the "patient had been ailing for about two weeks with abdominal pains, restlessness and general nervous irritability. Her mother gave her worm medicine which caused the passage of some worms but symptoms did not improve." One could think that the child had acrodynic symptoms before the worm medicine was given and that the latter was of no etiological importance. However, when the child recovered, the mother informed the author that she had been in the habit of giving the patient a worm candy about once a week for the past year. The situation was similar in case 41 of our series. This illustrates that worm treatments are often given injudiciously in certain areas and that the treatment mentioned in the case report may not be the first of its kind. In some reports an interval of several months seemed to lie between the mercurial treatment and the outbreak of the disease. This may be explained by the fact that ingested mercury can remain in the body for some time without any ill effects and then suddenly become toxic (see p. 347); or a worm treatment or a mercurial ointment may be mentioned by the parents only once in the history while a repetition of the treatment may appear irrelevant to them and not be reported.

Mercury and the Recent Literature on Acrodynia.—It has been mentioned before (p. 365) that Zahorsky in 1922 suspected mercury poisoning as the cause of acrodynia but dismissed the hypothesis, since cases were encountered in which no history of administration of mild mercurous chloride could be elicited. Davison [122] mentioned mercury as a suggested cause of acrodynia and attributes the suggestion to Dr. Lesesne Smith, Sr. In 1947 Fanconi, Botsztejn and Schenker [23] published an excellent study. Under the heading of rare late reactions after internal and external applications of mercury, they mentioned granulocytopenia, polyradiculoencephalitis and Feer's disease (acrodynia). They stated in regard to the last disease that according to their conception Feer's disease is a neuroallergic reaction to various noxae, mostly of an infectious nature. The specific symptoms of acrodynia are almost always preceded by a *Vorkrankheit,* which may be an infectious disease, a banal, somewhat insidious infection, recurrent diarrhea, etc. When reviewing their 120 histories of Feer's disease, they were struck by the frequency of worm treatments in the anamnesis. In 42 children one or repeated worm treatments had been given several weeks previously. The time relationship could not be established exactly in 34 cases; in several cases the symptoms of acrodynia began before the worm treatment; the medicine was given because the children were ill humored or complained of poorly defined ailments. However, in eight cases the worm

120. Mayerhofer and Dragišić.[58] Zahorsky.[58]

121. Currie.[45] Mayerhofer and Dragišć.[58] Selter.[54] Poinso and others.[119] Case 28 of our series.

122. Davison, W. C.: Compleat Pediatrician, Durham, N. C., Duke University Press, 1946; personal communication to the authors.

treatments preceded the acrodynic symptoms by several days or weeks; four children had a calomel disease, one child even twice, after the first and after the second worm treatments. These authors believed, therefore, that use of mild mercurous chloride can cause Feer's disease as a *Vorkrankheit,* similar to infectious noxae, and also in cases in which the hypersensitivity to mercury is not manifested as classic calomel disease. Feer's disease would be considered in these cases as a neuroallergic late reaction to mercury. These authors mentioned also two cases in which the disease followed external application of mercury. They wrote that this confirmed their supposition that a neuroallergic reaction may follow sensitization to mercury.

In May 1947 Bivings and Lewis [116c] diagnosed the disease of a 6-month old infant as acrodynia. Having knowledge of our findings of mercury in the urine of several children with acrodynia, these investigators obtained from the mother a history of administration of mild mercurous chloride to the child some weeks previously. In the urine of the infant 100 micrograms of mercury per 100 ml. (1,000 micrograms per liter) was found. On the basis of this finding Bivings and Lewis treated the child with dimercaprol (BAL), and within 19 days mercury disappeared from the urine and all clinical symptoms cleared except photophobia. This case was reported at the meeting of the Southern Pediatric Seminar, at Saluda, N. C., on July 14, 1947 and published in January 1948.[116c] In May 1948 Elmore [123] reported acrodynia in two infants who had received mild mercurous chloride in teething powders. Dramatic resolution of symptoms followed treatment with dimercaprol. The mercury determinations in the urine of these infants were made in the Kettering Laboratory in Cincinnati, and they are included in this study (cases 7 and 8). Our studies begun in 1945 were not published before May 1948.[16] They had been cited previously by Bivings and Lewis [116c] and Elmore,[123] as well as in an annotation in *The Lancet.*[108] In the urine of 20 children, clinically diagnosed as acrodynic, mercury was found in 18 instances, while the urine was free of it in two instances. Forty of 49 control persons had no mercury in the urine, eight had small amounts and only one child excreted appreciable amounts. This child had had mild mercurous chloride treatment previously. After discussing our findings as well as those of Bivings and Lewis, an annotation [124] in *The Lancet* of April 24, 1948 stated:

> The mothers of 10 children suffering from pink disease were questioned in London recently and in each case it was found that the child had had "teething powders," which generally contain calomel (or sometimes pulv. hydrarg. cum cret.) in considerable quantities.

In September 1948 Fanconi and Botsztejn [30] reported on 26 cases of acrodynia treated in the Children's Hospital, of Zurich, Switzerland, from 1946 to 1948. The parents of six of these children had not been questioned about mercury medication. In 19 of the 20 cases in which parents were questioned, mercury medication had preceded onset of the disease. Sixteen children had been given worm treatments of santonin and mild mercurous chloride, one child worm treatment and a mercurial ointment and two children mercurial ointments only. In December 1948

123. Elmore, S. E.: Ingestion of Mercury as a Probable Cause of Acrodynia and Its Treatment with Dimercaprol (BAL): Report of 2 Cases, Pediatrics **1**:643, 1948.

124. Pink Disease, Annotations, Lancet **1**:644, 1948.

Lefebvre [125] presented in Paris a case of typical acrodynia in a child 2½ years old who had undergone two worm treatments with a mercurial vermifuge and who showed acrodynia several days after the last treatment. In the urine 1 mg. (1,000 micrograms) of mercury per liter was found. Among 10 other cases of acrodynia in which mercury was not determined in the urine, questioning revealed that mild mercurous chloride contained in a vermifuge was given in seven cases. Additional cases of acrodynia of mercurial origin were reported by Bivings [116d] and by Baumann [28] in 1949.

These examples demonstrate that in most recent case reports of acrodynic patients mercurial medication could be shown to precede the onset of the disease.

Variety of Adverse Mercurial Reactions.—Adverse reactions to mercury may appear on the skin, on the mucous membranes, in the peripheral or central nervous system, in the kidneys and in the bones. They may be febrile or afebrile; they may last several days or many months. They may follow exposure to mercury immediately or after an interval of several weeks or months. They appear in the form of different disease pictures: acute dermatoses, calomel disease, stomatitis, gangrene in the oral cavity or of the phalanges, nephritis, nephrosis, granulocytopenia,[28] polyneuritis, Landry-Guillain-Barré syndrome, fibrillary chorea of Morvan and acrodynia. Most of these conditions have been discussed in previous sections, and it remains to discuss the relationship of the last three disorders.

It was mentioned before (p. 359) that symptoms of Landry-Guillain-Barré syndrome may develop in cases of acrodynia. In one patient of this series (case 27) who had acrodynia and Landry-Guillain-Barré syndrome exposure to as well as presence of mercury in the urine and in the kidneys could be proved. On the other hand, cases of Landry-Guillain-Barré syndrome without acrodynic symptoms have been shown to follow ingestion of mercurial drugs.[126] Thus mercury intoxication may assume the form of either acrodynia or Landry-Guillain-Barré syndrome or a combination of the two.[28]

In 1935 it was pointed out by Roger and Alliez [127] that Morvan's fibrillary chorea and infantile acrodynia had many symptoms in common. Patients with fibrillary chorea have, in addition to fibrillary muscular contractions, burning, lancinating, sometimes paroxysmal, pains; formication; hyperesthesia; abdominal colic without diarrhea; excessive perspiration, occasionally in the form of sudoral crises; pruritic rashes; red, shiny, swollen palms and soles; desquamation; anorexia; insomnia; irritability; anxiety, change of character; tendency to cry and complain, and confusion or delirium. In addition, some of the patients have salivation, stomatitis, conjunctivitis, muscular weakness, inability to stand or walk, loss of sphincter control, tachycardia, hypertension and albuminuria. There is no fever, and the condition lasts several weeks or months. Of 11 patients included in the report two died of the disease. Although all the patients were adults, the

125. Lefebvre, G.: Acrodynie infantile et toxi-allergie au mercure, Arch. franç. pédiat. **6**:82, 1949.

126. Leyden.[64e] Fanconi and others.[76e]

127. Roger, H., and Alliez, J.: La chorée fibrillaire de Morvan, Marseille- méd. **1**:333 and 377, 1935.

resemblance of fibrillary chorea to infantile acrodynia is striking indeed. Fibrillary muscular contractions seem to distinguish the two conditions. However, Roger and Alliez pointed out that myoclonic contractions have been repeatedly described in acrodynia and may be an alternative symptom for fibrillations. They mentioned briefly a boy, 14 years of age, who represented an intermediate case between fibrillary chorea and acrodynia, and case 4 of our series is apparently comparable to theirs.

It seemed worth while to study the medications which preceded the outbreak of this disease that resembles acrodynia in so many respects. Morvan's patient [98] had scabies six months before outbreak of the disease and was treated by inunctions with *onguent citrin,* a mercurial ointment (unguentum hydrargyri nitratis forte). Marked fibrillary contractions, lancinating pains, insomnia and diarrhea developed. There were increasing muscular weakness, excessive perspiration, tachycardia, albuminuria, swelling and redness of the hands, and, finally, delirium, coma and death. The patient of Colin and Dutil [66] received 39 injections of mercuric cyanide in the treatment of sympathetic ophthalmitis. Two weeks after the last injection the patient complained of pains in all parts of the body, could not sleep and lost his appetite. He showed fibrillary contractions in all muscles except those of the face. He was completely dejected and cried like a child. Other symptoms were abdominal colic without diarrhea and impairment of gait. The patient of Roger, Longchampt and Alliez [128] had orchitis and was treated with a mercurial ointment; one month after the onset of the orchitis pains and fibrillary contractions developed. He suffered from muscular weakness, insomnia, excessive perspiration and irritability. The hands were somewhat red, and desquamation was seen on the palms. Recovery occurred after six months. The patients of Roger, Pekelis and Alliez [129] and of Roger, Alliez and Jouve [130] also had orchitis before the outbreak of fibrillary chorea. No information is available concerning the treatment of their orchitis, but it is not unlikely that they too were treated with a mercurial ointment, since this has been the conventional treatment of orchitis and epididymitis in the past.[131] In the patient of Porot [99] the outbreak of fibrillary chorea was preceded by a syphilitic infection for which he was hospitalized *dans un service special.* Since this was in 1906, there can be little doubt that this patient received mercurial treatment before onset of the disease. For two patients [132] no information is given concerning a preceding illness or medication.

---

128. Roger, H.; Longchampt, J., and Alliez, J.: Considérations étiologiques et pathogéniques sur la chorée fibrillaire de Morvan, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:677, 1935.

129. Roger, H.; Pekelis, E., and Alliez, J.: La chorée fibrillaire de Morvan: Sa localisation au niveau des centres neurovégétatif de la base; ses relations avec l'acrodynie infantile, Rev. neurol. **1**:248, 1934.

130. Roger, H.; Alliez, J., and Jouve, A.: Chorée fibrillaire de Morvan compliquée de diplégie faciale, de troubles psychiques et d'un syndrome de Landry mortel, Gaz. d. hôp. **108**:1137, 1935.

131. Finger, E.: Die Syphilis und die venerischen Krankheiten, Leipzig, F. Deuticke, 1896.

132. Mollaret, P.: Un cas de chorée fibrillaire de Morvan, Rev. neurol. **2**:552, 1930. Lambrechts, A.: Contribution à l'étude de la chorée fibrillaire de Morvan, ibid. **2**:115, 1934.

Two patients of Chavany and Chaignot[133] and the patient of Gernez[134] displayed fibrillary chorea following gold therapy administered for tuberculosis. The description of the disease picture in the latter patient reads like one of acrodynia. He had a vesicular rash, excessive perspiration, intolerable burning sensations on the soles, pains, fibrillary contractions and tremor, extreme muscular weakness without paralysis, slow and incoordinated movements, anorexia, anxiety and confusion. The disease lasted for six months and ended in recovery. That a disease picture resembling acrodynia so closely can be brought on by the administration of gold compounds is important in the discussion of the next section.

Toxic Substances Other than Mercury in the Causation of Acrodynia.—The fact that we consider exposure to mercury the most important factor in the causation of acrodynia does not rule out the possibility that similar symptom complexes can be caused by other toxic substances. Acrodynic disease pictures have been attributed to exposure to arsenic in several instances.[135] Of an early and fatal case of acrodynia we were told[7] that no other medicament was given than "brown mixture" which contains antimony. In three cases of *Morvan's fibrillary* chorea which simulated acrodynia in many respects, gold therapy preceded the onset of the disease. Salivation and dermatitis exfoliativa occur as manifestations of idiosyncrasy to iodine,[136] and many other drug reactions simulate mild forms of acrodynia in certain respects. Ergotism and ustilaginism[137] produce acrodynia-like disorders, and it is possible that other toxic substances not yet recognized behave likewise. However, at present and in our material acrodynia appears to be of mercurial origin in the majority of instances, and we believe that the same holds true in other areas where teething powders, worm medicines and other mercury-containing preparations are widely used.

Treatment and Prevention of Acrodynia.—Numerous treatments have been recommended for patients with acrodynia. It is not possible to discuss here all the therapeutic measures which have been advocated, and it is significant that success has been claimed for the most diverse methods. It is known that acrodynia may vary in its manifestations from the hardly recognizable *formes frustes* to the most characteristic severe and fatal cases. The duration varies from a few weeks to many months and even years.[138] In these circumstances evaluation of different methods of treatment is difficult, and all recommended therapeutic measures have failed so far when tested in severe cases.

Only one of these recommended treatments will be discussed here, since it is aimed specifically at the mercurial origin of acrodynia. Based on our finding of

133. Chavany, J. A., and Chaignot, A.: Contribution à l'étude des accidents nerveux de la chrysothérapie: Syndrome douloureux, anxieux et insomniaque avec présence de secousses fibrillaires à peu près généralisées, Presse méd. **42**:478, 1934.

134. Gernez, C.: Les accidents neuro-psychiques de l'aurothérapie, Rev. de la tuberc. **1**:386, 1935.

135. Petrén.[4] Péhu and Ardisson.[5] Meyer and Weise.[8] Calvin and Taylor.[9]

136. Cushny, A. R.: Pharmacology and Therapeutics, ed. 13, Philadelphia, Lea & Febiger, 1947.

137. Mayerhofer.[2c] Debré and Nevot.[3]

138. Lévy and Schneider.[77k] Clément, R., and Stoopen, E.: Fréquence des formes prolongées et des séquelles de l'acrodynie infantile, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:1771, 1938.

mercury in the urine of children with acrodynia, Bivings and Lewis [116c] recommended the use of dimercaprol for the treatment of this disease. This recommendation was a logical step since the drug has been used with excellent results in the treatment of arsenic and mercurial poisoning. The patient of Bivings and Lewis had received 12 doses of mild mercurous chloride and rhubarb several weeks before the outbreak of the disease, and 1,000 micrograms of mercury per liter was found in her urine. Treatment consisted of intramuscular injections of a 10 per cent solution of dimercaprol in oil preceded by 0.5 ml. of 2 per cent procaine (novocain®) hydrochloride. Three milligrams per kilogram of body weight was given every four hours for 48 hours, than every six hours for 24 hours, then every 12 hours for seven days. By the end of the fourth day of treatment the skin of the hands seemed less pink and warmer, and by the sixth day the photophobia was definitely improved. Nine days after the treatment was begun there was still an excretion of 600 micrograms per liter of mercury in the urine. Eleven days later the urine was reported to be free of mercury. Improvement continued, but the child still had photophobia, abdominal pain and irritability, although the urine was free of mercury.

This report was followed soon by a publication by Elmore,[123] who treated two children with dimercaprol who had acquired acrodynia following administration of teething powders containing mild mercurous chloride. Within six days definite improvement began, and the children appeared well after two weeks. Fanconi and Botsztejn [30] treated three acrodynic children with dimercaprol and observed an accelerated recovery. Bivings [116d] summarized the results of dimercaprol therapy in 15 patients with acrodynia and observed prompt improvement or recovery in 11 and slow improvement in four.

Twenty-three patients of our series were treated with dimercaprol. The results are hard to evaluate because the severity of the disease varied and the effect was judged by different observers. In some patients treatment was given soon after onset of the disease and in others at later stages. Improvement was rapid in 10 patients, gradual in nine and slow in two. Two patients, both with the severe disease, died in spite of dimercaprol treatment. Untoward, shocklike reactions during dimercaprol treatment occurred in three children and in one of them twice.[139]

It is not possible to draw definite conclusions from these results in regard to the effect of dimercaprol therapy on the course of acrodynia. It can hardly be expected that in cases of long standing the effect of the drug will be as impressive as in cases of acute mercury poisoning.

Awareness of the etiological relationship between acrodynia and mercury points the way toward prevention. Teething powders, the most frequent cause of acrodynia in our series, are apparently completely useless and should be abandoned. Santonin and mild mercurous chloride and other vermifuges containing mild mercurous chloride are being replaced by more effective agents. Nonmercurial antisyphilitic drugs and nonmercurial disinfectants and antibacterial ointments have become available. Recognition of the hazard in a manner leading to thoughtful avoidance whenever possible of mercurial medication in infants and small children holds the promise of effective prophylaxis.

---

139. Beale, J. D., Jr., and Schrum, D. I.: Serious Toxic Reaction Associated with Administration of BAL, J. Pediat. **35**:498, 1949.

SUMMARY

It is suggested that exposure to mercury of hypersensitive children is the most important factor in the causation of infantile acrodynia. Exposure to mercury was demonstrated in 38 of 41 acrodynic children by the presence of the metal in their urine. In 23 of these children mild mercurous chloride (calomel), teething powders or worm pills containing mild mercurous chloride, ammoniated mercury ointment and mercury bichloride used for rinsing diapers were ascertained to be the sources of mercury. Idiosyncrasy to mercury which manifests itself in acrodynia exists particularly in infants and small children, while older children and adults have a higher tolerance. Other factors which lower tolerance undoubtedly exist, but they are unknown at present. Hypersensitivity to mercury can manifest itself in many forms, and acrodynia is one of them. Acrodynia resembles recognized manifestations of mercury poisoning in many respects and differs from them in others. Transitional states between acrodynia and various established forms of mercury poisoning exist. It is possible that metals, drugs and toxic substances other than mercury produce disease pictures resembling acrodynia. The effectiveness of dimercaprol (BAL) in the treatment of acrodynia could not be clearly demonstrated in the series of cases presented. It is possible that in cases of long standing the effect is not so striking as in cases of acute mercury poisoning.

Special Article

THE AMERICAN JOURNAL OF DISEASES OF CHILDREN

CLIFFORD G. GRULEE, M.D.
EVANSTON, ILL.

THE DECEMBER 1950 issue was the last of the eightieth volume of the AMERICAN JOURNAL OF DISEASES OF CHILDREN. The first volume appeared in 1911.

When the Board of Trustees of the American Medical Association met on Feb. 4, 1910, Dr. Isaac Abt and Dr. F. S. Churchill, on behalf of a number of pediatricians, presented the following communication requesting the publication by the Association of a periodical devoted to pediatrics:

Appreciating the need in America of a journal of pediatrics published and entirely controlled by the medical profession; impressed, morever, by the high character and success of the *Archives of Internal Medicine* established by your Board two years ago, we respectfully request that you establish a journal of pediatrics on somewhat similar lines.

There is at present no journal in the English language devoted to this important branch of medicine, which at all corresponds, for example, to the *Jahrbuch für Kinderheilkunde* published in Germany. The large and increasing number of articles relating to pediatrics which are constantly appearing in *The Journal of the American Medical Association* and other general medical journals is evidence of the amount of creditable work in pediatrics which is being done in this country, and of the abundance of material which is available for such a publication as we propose. Such a journal would command the support of all who are engaged in pediatric practice, teaching and research in the United States, and would make a strong appeal to the general practitioner much of whose practice is of necessity among children.

Such a journal should give prominence to articles embodying research in pediatrics, but should include, as well, good articles of a practical character including even clinical memoranda—abstracts of important discussions in the pediatric societies, all carefully selected and edited, and, finally, carefully prepared abstracts of the pediatric literature of the world. It should carry no advertisements.

It is suggested that if this request be favorably considered by you, that you select an Advisory Committee of ten or twelve pediatrists, representatives of the leading medical centers, which committee shall consider and report to your Board, as soon as practicable, upon the essential details of this proposed journal such as the name, frequency of issue (a bimonthly has been suggested), size, subscription price, character and arrangement of contents, etc., and to nominate an editorial board of four to six pediatrists, who shall have editorial control of the journal, in a manner similar to that of the Editorial Board of the *Archives of Internal Medicine*.

Should the proposed journal be established we pledge our earnest and continued support as contributors and subscribers.

In response to that petition, the Board of Trustees appointed a committee of eleven to secure information in regard to the publication by

the American Medical Association of a periodical devoted to pediatrics. The committee consisted of Drs. Abraham Jacobi, L. Emmett Holt, Thomas Southworth and G. R. Pisek, of New York; T. M. Rotch, of Boston; Edwin E. Graham and J. P. C. Griffith, of Philadelphia, and W. J. Butler, Isaac A. Abt, J. N. Dodson and Frank Spooner Churchill, of Chicago.

At the meeting of the Board of Trustees on June 6, 1910, the following letter was presented from the Section on Diseases of Children.

Gentlemen:

At a meeting of the Section on Diseases of Children, June 7, 1910, it was moved and after due discussion carried, that the Section approve the recommendation to the Board of Trustees for the publication of a special journal devoted to the diseases of children and that the matter be referred to the Executive Committee of the Section with power to act.

A meeting of the Executive Committee of the Section on Diseases of Children was held June 8, 1910, at 8:30 a.m., in conjunction with the Committee appointed by the Board of Trustees.

Doctor Snyder, Chairman of the Executive Committee, first called to order a meeting of that Committee.

Doctor Graham moved, and the motion was carried, that the Executive Committee transmit to the Board of Trustees the action of the Section in approving the establishment of a special journal.

The Executive Committee then adjourned.

Doctor Abt, Chairman, called to order a meeting of the joint committees.

A motion was made, and carried, to accept the report of a subcommittee on names of the proposed journal and to recommend to the Trustees that it be called *The American Journal of Diseases of Children.*

The following recommendations were also adopted: That the periodical should contain original articles, abstracts and occasional complete reviews by men appointed by the Editorial Board; that it should begin as a bi-monthly of approximately 64 pages an issue; that it should be about the size of the *Archives of Pediatrics;* that the Editors shall choose their own chairman, and that the subscription price be referred to the Trustees.

The joint meeting then adjourned.

The Executive Committee of the Section on Diseases of Children reconvened at 9:30 a.m., and voted to submit the following names to the Board of Trustees for selection of an Editorial Board:

Dr. Abraham Jacobi, New York
Dr. John Lovett Morse, Boston
Dr. Edwin E. Graham, Philadelphia
Dr. Frank Spooner Churchill, Chicago
Dr. J. H. M. Knox, Baltimore
Dr. G. R. Pisek, New York
Dr. Isaac A. Abt, Chicago
Dr. W. J. Butler, Chicago
Dr. J. R. Snyder, Birmingham
Dr. J. P. C. Griffith, Philadelphia
Dr. J. M. McClanahan, Omaha
Dr. L. Emmett Holt, New York

Respectfully submitted

Executive Committee Section on Diseases of Children

J. Ross Snyder
Edwin E. Graham
Thomas S. Southworth

At that meeting—June 6, 1910—the Board of Trustees authorized the publication of a periodical to be known as the AMERICAN JOURNAL OF DISEASES OF CHILDREN. The selection of men to constitute the Editorial Board, however, was postponed until October, at which time the following Board was elected:

Drs. Abraham Jacobi, of New York, and W. Fitch Cheney, of San Francisco—each for two years.

Drs. John Howland, of New York, and John Lovett Morse, of Boston—each for four years.

Drs. F. S. Churchill, of Chicago, and Edwin E. Graham, of Philadelphia—each for six years.

Dr. George H. Simmons was appointed managing editor to represent the Board of Trustees.

The edict of the Board of Trustees at this time was that the periodical was not to carry any advertisements.

The introduction of volume 1 was written by Abraham Jacobi, and the first articles were by Fetterolf and Gittings, the latter of whom was subsequently an Editor of the JOURNAL. Of the original Editorial Board, not a single one is now alive, Dr. Churchill having died in 1946.

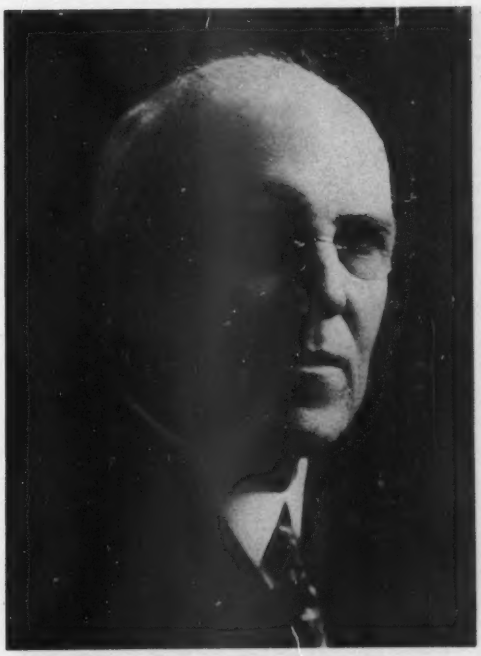
In the first volume appeared names of physicians who have made pediatric history—L. Emmett Holt Sr., Martha Wollstein, I. A. Abt, Kerley, Schloss, Brennemann, Alfred Hess, Morse and Talbot. Most of the articles were clinical. However, the pace for future volumes was set by the scientific articles of Schloss, Courtney and Gittings. In this first volume an article in Progress in Pediatrics provided selected abstracts.

Volume 2, which appeared in July 1911, had added such names as Fife, Veeder, Thomas Morgan Rotch, Howland, Koplick, J. H. M. Knox, Harry Shaw, Sedgwick and Schlutz and Julius Hess, in his first article in the JOURNAL on prematurity. News notes appeared for the first time in August 1911, and Progress in Pediatrics was changed to composite reviews. This year set the type of the future JOURNAL, and, although at times there was a change in the composition of the JOURNAL, it reverted in time to this arrangement, consisting of original papers, Progress in Pediatrics, abstracts and news notes. Later other features were added.

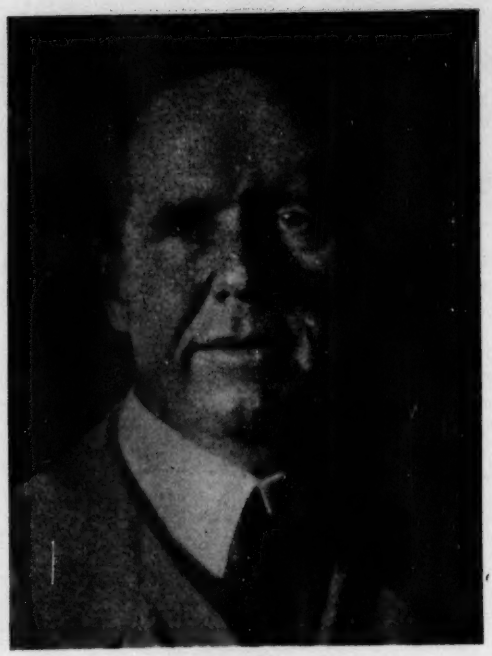
In 1911 Dr. Cheney resigned from the Editorial Board and was replaced by Dr. David M. Cowie.

In volume 3 (1912) the first article by a foreign contributor appeared. This was by E. Plauchu, Professor of Obstetrics, of Lyons, France, and was on "Resuscitation of Asphyxiated Infants by the Insufflation Method of Meltzer and Auer." In February of this year appeared the index of current literature, which was not continued for long, and in March there was an article by Ad Czerny on the "Atrophy of Infants." The first of May Michael's most comprehensive résumés on tuberculosis appeared in this volume, and others appeared for many years until her death. They were at times an outstanding feature of

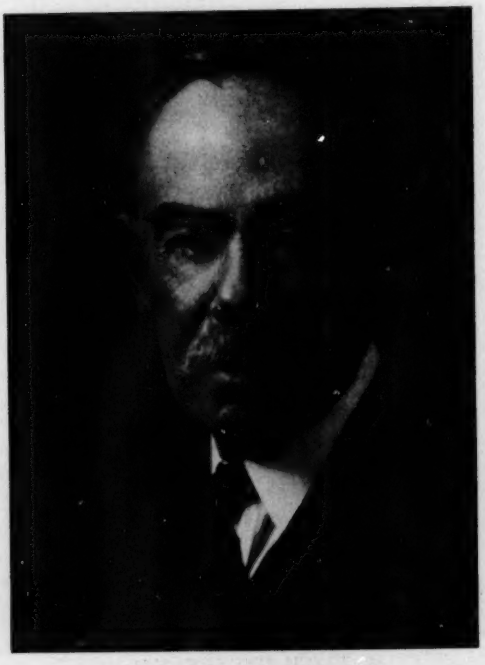
ABRAHAM JACOBI, M.D.



W. FITCH CHENEY, M.D.



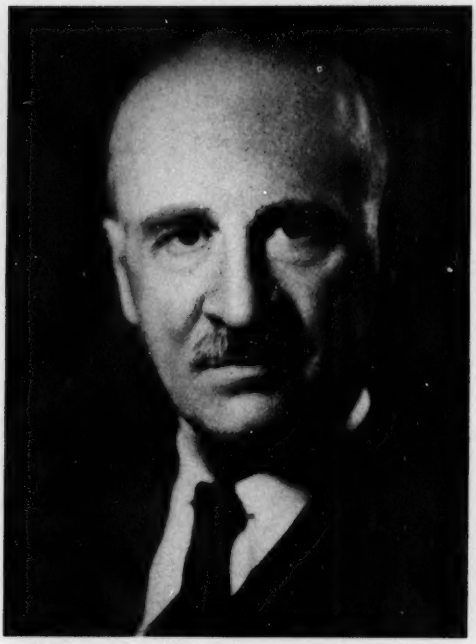
JOHN HOWLAND, M.D.



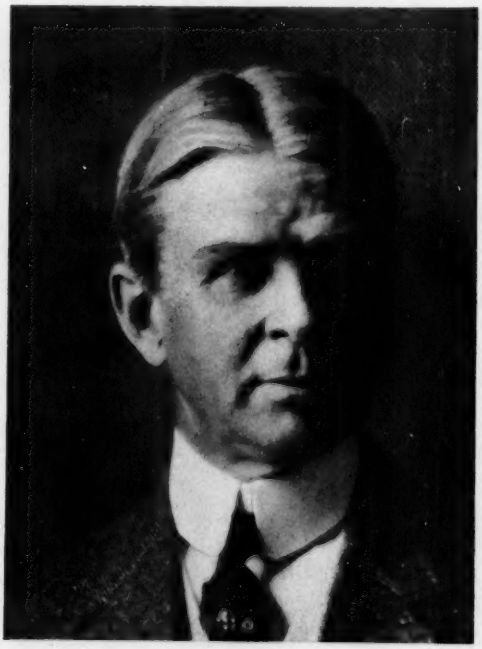
JOHN LOVETT MORSE, M.D.

FRANK SPOONER CHURCHILL, M.D.

E. E. GRAHAM, M.D.



DAVID M. COWIE, M.D.



L. EMMETT HOLT, M.D.

the JOURNAL. An article by Churchill in this volume was the first that the Chief Editor had contributed. In the fall of 1912, the name of Kenneth Blackfan as a contributor first appeared, a man who was to become later one of the outstanding figures in American pediatrics. There also appeared at this time the outstanding article by Benedict and Talbot on metabolism which was the forerunner of Talbot's fundamental studies on this subject. In this number for the first time appeared an article by John Ruhräh.

Dr. Abraham Jacobi was replaced on the Editorial Board by Dr. L. Emmett Holt Sr. in 1913. In volume 5 appeared the names as contributors of such well known figures in pediatrics as H. C. Carpenter, La Fetra, Richard M. Smith, DeBuys, Josephine Baker and Maynard Ladd, and in the May number was published the first of the Latin American contributions of Melilo Leitão, of Rio de Janeiro. In the fall of that year one notices the names of Langley Porter, Northrup, Blackader, Alan Brown and Zahorsky.

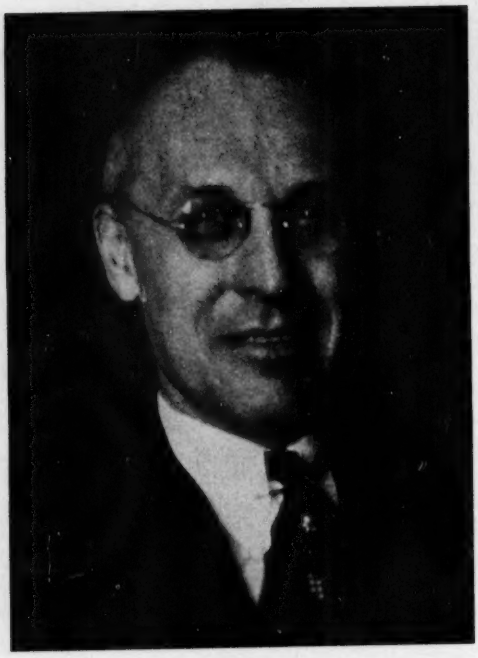
The first World War had not yet affected conditions in this country and seemed far away, and the work in pediatrics continued to advance. It was in volume 7 (1914) that observations by Alfred Hess on stomach, pylorus and use of the duodenal catheter first appeared, and Philip Van Ingen contributed an article on "Progress in Infant Welfare Work."

In volume 8, of the same year, Benedict and Talbot began their series of articles on respiratory exchange. In this year for the first time articles by Chapin, Faber and Jeans appeared, and two outstanding articles, one by Alfred Hess on "Infantile Scurvy" and the second, by Dandy and Blackfan, on "Internal Hydrocephalus," were published. In volume 8 obituaries appeared for the first time, those of Rotch, Putnam and Forchheimer.

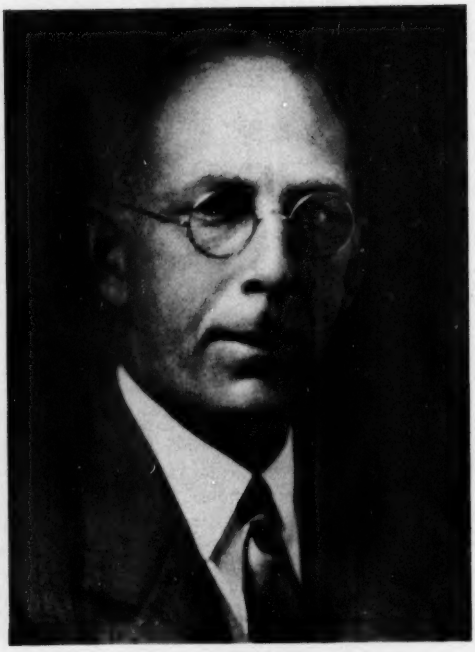
In volume 9 (1915) there was evidenced more intensive interest in chemical and biochemical problems. Murlin and Hoobler published an article on energy metabolism, and Holt, Courtney and Fales began their series of articles (which were to continue for several years) on the chemical composition of stools. Here, too, first appeared an article by Gamble.

Volume 10 had articles by Helmholz and Gerstenberger. Volume 11 contained an article by Howland and Marriott on "Acidosis Occurring with Diarrhea." This is the first time that these two eminent pediatricians appeared jointly as authors of an article.

In the next volume (1916) Helmholz began his study on pyelitis. The name of Edwards A. Park first appeared among the reviewers and that of A. Graeme Mitchell among the contributors. During 1917 and 1918 the effect of the war apparently made a great deal of difference. A number of papers on chemical subjects did appear in volume 13 (1917) but the size of the JOURNAL was reduced, and the effect of the war is shown by the fact that in the October issue of volume 16 (1918) there were several articles dealing with the work of the Children's Bureau of the American Red Cross in France.



HENRY F. HELMHOLZ, M.D.



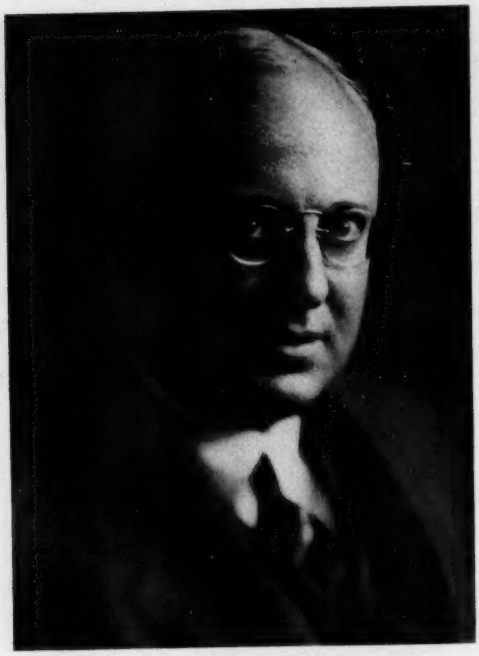
FRITZ B. TALBOT, M.D.

In 1919 Dr. Churchill left Chicago to make his home in Massachusetts and was replaced on the Editorial Board by Dr. Henry F. Helmholz, who became the Chief Editor. In volume 18 (November 1919) there appeared the first monograph by Park and McClure on the thymus. In 1920 John L. Morse was replaced by Fritz B. Talbot on the Board, and in volume 20, of that year, appeared the first article by Grover Powers.

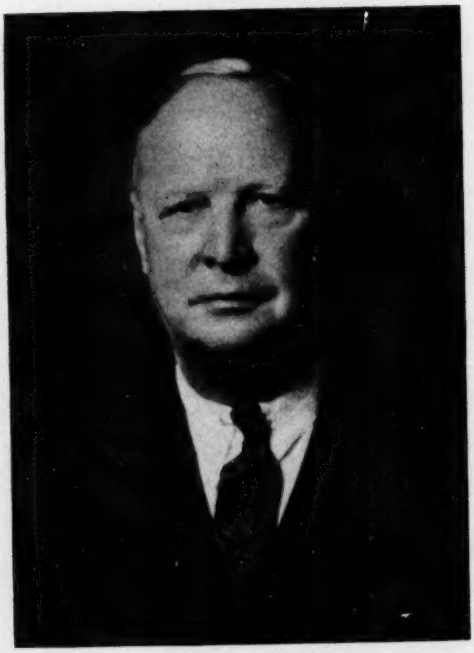
In volume 22 (1921) there appeared two articles which were definitely to influence the practice of pediatrics. The first was by Cooke, on the ammoniacal diaper, and the second was by Brennemann, on abdominal pain. These two articles have shown their practicality throughout the years and have resulted in much benefit to pediatrics. In volume 24 (1922) appeared the first book reviews; at the same time Dr. E. E. Graham was replaced by Dr. W. McKim Marriott. In volume 25 (1923) the names of Toomey and L. Emmett Holt Jr. appeared for the first time, and in volume 26, those of Weech and James Wilson, who are at present on the Editorial Board.

In 1924 Dr. Helmholz went to the Mayo Clinic and Dr. L. Emmett Holt Sr. died. Dr. David M. Cowie was succeeded by Dr. Clifford G. Grulee and Dr. L. Emmett Holt Sr. by Dr. Oscar M. Schloss. At this time the Trustees of the American Medical Association requested a change, an enlargement of the scope of the JOURNAL. The résumés were continued, but, unfortunately, those on tuberculosis ceased, owing to the death of May Michael. Book Reviews, News and Comment and Society Transactions began to appear, and Abstracts from Current Literature were stressed. An attempt was made to cover the current literature on pediatrics, an attempt which was fairly successful because of the active cooperation of the younger men who were going into pediatrics and of the older men who could find the time for abstracting.

In volume 28, October 1924, the transactions of the American Pediatric Society first appeared. These had previously appeared in the *Archives of Pediatrics*, but, owing to a change in policy on the part of the Society, it was decided to publish the papers in abstract, together with the discussions in the AMERICAN JOURNAL OF DISEASES OF CHILDREN. In this number, it is interesting to note, W. H. Parke and Zingher published an article on diphtheria immunization in New York city, which was most timely; it is probably due to these two authors that there has been such an extensive use of immunization procedures in this country. Immunization procedures, which are now adopted by all the armies of the world, have not been used so extensively in any other country as they have in the United States. Apparently the period of adolescence had been gradually outgrown, and the JOURNAL was beginning to take on its full maturity. It is doubtful that this meant that more outstanding articles were to appear, since many of the articles mentioned may be regarded as some of the milestones in American pediatrics. However, from now on the JOURNAL took a more scientific turn. After the war and as a consequence of the resulting prosperity, more time and money were devoted to scientific investigation. This was taken advan-



W. McKIM MARRIOTT, M.D.



CLIFFORD G. GRULEE, M.D.

OSCAR M. SCHLOSS, M.D.

L. R. DEBUYS, M.D.

tage of by pediatricians, and most of the scientific articles were published in the AMERICAN JOURNAL OF DISEASES OF CHILDREN. For instance, the respiratory metabolism studies of Sam Levine and his co-workers appeared in volume 31 (1926), and in volume 32 (1926) Hartmann began his chemical studies, Aldrich his work on nephritis and Powers his work on intestinal intoxication, the name of Joseph Stokes first appeared and, in addition, the pediatric profession had a grave loss. John Howland, who had meant so much to American pediatrics, died before his time but not before he had made a profound impression on American pediatrics and had founded a new school in that branch of medicine. It was in this year that L. R. DeBuys joined the Editorial Board.

In volume 33 (1927) Sanford's first studies on the newborn appeared, and an article by Lynne A. Hoag, who started with so much promise, first appeared here. His untimely death, unfortunately, occurred not much later. In volume 33 (March 1927) a Directory of Pediatric Societies first apeared. In volume 34, of the same year, appeared the outstanding article by Thomas Cooley, of Detroit, on "Anemia in Children." This was the original article on so-called Cooley's anemia. In this volume, too, the names of McIntosh, Casparis and McQuarrie appeared in the list of authors. In volume 35, the first volume for 1928, Ruhräh started his pediatric biographies, which carried through for several years, and in the second volume for that year appeared the article by Clara Davis on the "Self Selection of Diets by Newly Weaned Infants," and Wallgren's first article on tuberculosis. Darrow appeared as an author for the first time. John C. Gittings was taken on the Editorial Board in this year. McQuarrie's article on water metabolism in epilepsy, appearing in volume 38 (1929), has received a great deal of attention.

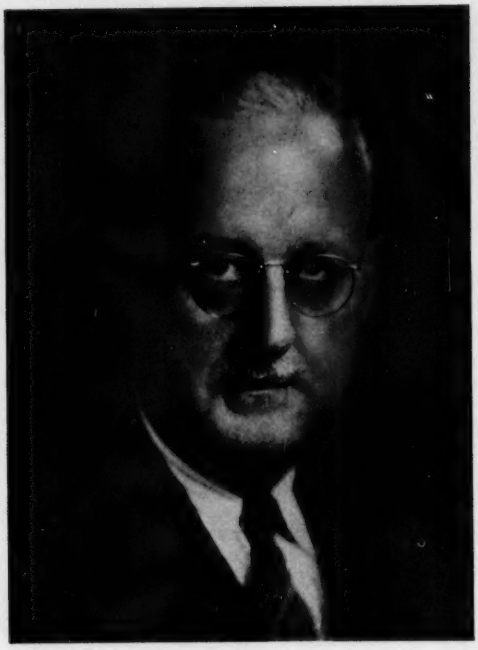
Soon after this the JOURNAL began to expand in size until it became almost unwieldy. Volume 39 (1930) contained 1,692 pages, the largest volume that was published.

The first of Icie Macy's studies on human milk appeared in volume 42 (1931), and the succeeding years were marked by the presentation by her and her co-workers of many different subjects, especially on chemical analysis. The first report of the American Board of Pediatrics was published in volume 51 (1936). In 1937 Dr. McKim Marriott died, and his unexpired term was filled by Dr. A. G. Mitchell. In 1938, in Progress in Pediatrics, appeared an outstanding article by Dorothy H. Andersen on "Cystic Fibrosis of the Pancreas," and in the next year (volume 57) the article by McIntosh and Donovan on the "Disturbances of Rotation of the Intestinal Tract." Volume 59 (1938) contained the article by Hilde Bruch on "Obesity in Childhood." These three articles were most stimulating. In 1939 Dr. Horton Casparis replaced Dr. L. R. DeBuys on the Board, and in 1940 Dr. F. S. Smyth succeeded Dr. John Gittings. In 1942 the obituary of Dr. Kenneth Blackfan appeared, and this volume, too, marked our first year in World War II.

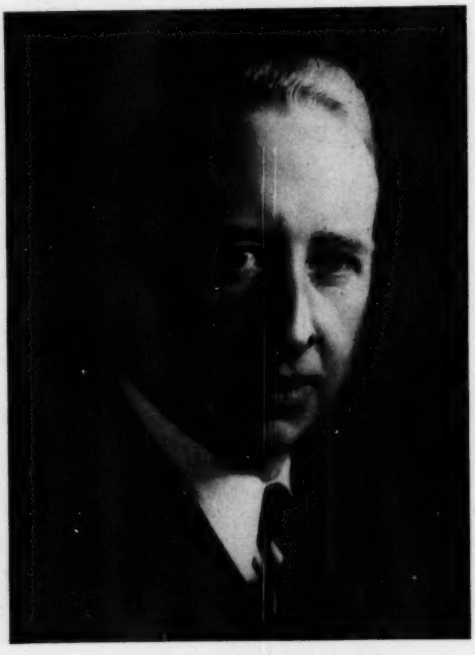
The JOURNAL by this time had been reduced to 1,200 pages a volume. In the latter part of this year the obituary of Casparis appeared. The

JOHN C. GITTINGS, M.D.

A. GRAEME MITCHELL, M.D.



HORTON CASPARIS, M.D.



FRANCIS SCOTT SMYTH, M.D.

year 1943 was marked as the year of the beginning of shortages, and the format was changed to a larger page and more closely spaced lines. Of course, during this period the abstracts were reduced in number owing to the fact that there was almost a cessation of scientific work in the rest of the world. In volume 65 (1943) appeared the first of Warkany's articles on malformations induced by diet, and in volume 66 the last of Brennemann's articles. In volume 66, too, appeared the outstanding contribution of Hattie E. Alexander on the treatment of influenzal meningitis. Volume 67 (1944) showed the effect of the war in that in the February issue the JOURNAL was smaller, not in the actual amount of material, but in that it was printed in two column style with smaller type and thinner paper. Brennemann's obituary appeared in volume 68 (1944), and in volume 69 (1945) appeared the first of the series of articles on the celiac syndrome by Dorothy H. Andersen. In 1943 Dr. James L. Wilson had succeeded to the Board on the death of Dr. Casparis, and in the same year Dr. A. A. Weech had replaced Dr. Mitchell, who had died in that year.

In July 1945 (volume 70), Dr. Jaso, of Madrid, Spain, submitted his article on the Laurence-Moon-Biedl syndrome, and Getz, from Panamá, Republic of Panama, an article on intestinal parasites. The outstanding articles in the August issue were the one by Gross, "Arterial Embolism and Thrombosis in Infancy," and Andersen's contribution on celiac disease. In the September issue appeared a continuation of the articles by Icie Macy Hoobler on the chemical composition of breast milk. In the October issue there was an obituary for William Mulherin. The November-December number had articles by Wallgren, of Stockholm, Sweden, Christie and Coburn and the obituary of C. G. Kerley.

In 1946 volume 71 returned to the original form. In January there were an article on erythroblastosis by Wiener and the obituary of T. B. Cooley. In February Bakwin's paper on behavior problems, and in March Zuelzer's study on megaloblastic anemia and the obituary of Frank S. Churchill were presented. In April there was the article of Francis Scott Smyth on periosteal reaction (a new syndrome). In the May issue appeared the Rachford lecture by Senn, and in June another article by Gross on congenital diaphragmatic hernia. In the July issue of volume 72, Aldrich's presidential address to the American Pediatric Society was published and the articles by Dorothy Andersen on the celiac syndrome were continued. In October Peterman had an article on convulsions, and in December Platou and Hansen had one on the use of penicillin in the treatment of congenital syphilis.

In the January 1947 issue (volume 73) appeared an article by Hansen on "Eczema and Essential Fatty Acids," and in April the articles by Rapoport and Dodd on infantile diarrhea and by Gordon on prematurity. In May there were articles by Toomey, Benjamin Kramer and Hoyne, and in June a symposium on prematurity by Samuel Levine, Julius Hess, Stewart Clifford and H. H. Gordon. In volume 74 (1947) appeared the presidential address to the American Pediatric Society by Harold Faber, and Joseph A. Johnston continued his study on growth. Johnston's name also appears in the October issue over

JAMES L. WILSON, M.D.

A. A. WEECH, M.D.

an article on the "Nutritional Requirement of the Adolescent and Its Relation to the Development of Disease," while Sweet wrote on body mechanics. In November Caffey presented his article on the syndrome of prenatal thickening of tubular bones. In December Bakwin and his associates reported on niacin deficiency and Rapoport on electrolytes, and there was an article from Japan.

In the January issue of volume 75 (1948) there was an article by Toomey on poliomyelitis, and Zuelzer and Wilson had a study on intestinal obstruction of neurogenic basis. In April an article appeared by Aldrich on reflexes of the newborn and one by John M. Adams on "Congenital Pneumonitis in Newborn Infants." One of the reviews in Progress in Pediatrics was by Cornelia de Lange, of Amsterdam, on pancreatic cysts. In May Parmelee and his co-workers presented a paper on acidosis in premature infants. The June issue included a paper by Debré, of Paris, on "Toxic Effects of Overdosage of Vitamin D_2 in Children" and one by Lozoya, of México, D. F., Mexico, on typhoid perforations. In this issue there appeared the obituary of Samuel McClintock Hamill.

Volume 77 (1949) contained contributions by Béla Schick and Abraham Levinson. In volume 78 the July 1949 issue included an article by Toomey, and in the November issue there were articles from the Netherlands, Scotland and the Philippines. The December issue contained the obituary of Frederick F. Tisdall.

Volume 79 (1950) showed the increase in the abstracts to 50 pages. At this time, Dr. Robert B. Lawson, from Winston-Salem, N. C., joined the Editoral Board, replacing Dr. Fritz Talbot, who resigned. In the January issue appeared an article by Clement Smith on the physiology of anoxia of the newborn and the first of the articles on the pancreas by Véghelyi, of Budapest, Hungary. In the March issue Johnston and his co-workers had an article on tuberculosis. There were also articles from Sweden and from Hungary. In the April issue appeared the obituary of John A. Toomey. The May issue had an article from Hungary and the June issue one from Israel.

Volume 80 began in July 1950. May and his co-workers contributed an article on megaloblastic anemia in the August issue. The presidential address to the American Pediatric Society, given by Jeans, was in the September issue. The October issue appeared in a different cover. The JOURNAL was designated the A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN in blue ink on the white cover, other printed matter being black. Instead of occupying the back cover, the table of contents was on the page before the first article.

The October issue contained another of Johnston's studies on growth. In November, Clement Smith and his colleagues continued their work on respiration in the newborn and premature infant and Diamond and his co-workers contributed one of their series of articles on erythroblastosis fetalis. In the December issue there was a study from Chile by Meneghello and his associates on liver steatosis and an article from Israel by Matoth.

This is the chronicle of the AMERICAN JOURNAL OF DISEASES OF CHILDREN. It should be borne in mind, of course, that in the making of a list of significant contributions my selections might not be approved by some of my colleagues, and the future developments of pediatrics might not confirm my judgments. Opinions differ, and it is oftentimes hard to tell what will and what will not be of outstanding importance.

Many young pediatricians in this country are showing rapid development. Their names will probably be well known in a few years. I

ROBERT B. LAWSON, M.D.

do not pretend to have the ability to foresee who will and who will not become noted. I have undoubtedly left out the names of many young men whose work will lead to their recognition as leading pediatricians. This is unavoidable, and to such young men I wish to offer my apologies.

The Editorial Board in December 1950 was constituted as follows:

Dr. A. A. Weech.....1951 Dr. Clifford G. Grulee.....1953
Dr. Francis Scott Smyth....1952 Dr. Oscar M. Schloss.....1954
Dr. H. F. Helmholz.....1952 Dr. Robert B. Lawson.....1955
Dr. James Leroy Wilson.....1956

The AMERICAN JOURNAL OF DISEASES OF CHILDREN has not been, in one sense, a national journal. In looking through the numbers one finds contributions from all over the world: In addition to Canada, whose pediatricians have made many contributions, England, France, Germany, Russia, Italy, Holland, Sweden, Denmark, Norway, Spain, Greece, Poland, Japan, China, Netherlands East Indies (Indonesia), Brazil, Argentina, Chile, Cuba, Mexico and Israel are among the lands whose pediatricians have contributed to the success of this JOURNAL. Throughout the years it has maintained a high standard, accepting only those articles which were of high scientific value or definite clinical import. It has attempted to cover the literature of the world in its abstracts and has, now and then, had articles of a definitely cultural value, such as Ruhräh's articles on pediatric biographies and on pediatrics in art. For the last several years, with the growth of American medicine, it has probably held the outstanding position in pediatrics in the world. Repeatedly I have been told so by foreign observers. It has come through two World Wars without lowering its standards, and, while it has at times been reduced in size, it has never accepted material which could be regarded as "padding." There have been times when the criticism has been raised that the JOURNAL was not sufficiently scientific and that it should contain only scientific articles. Those who maintain such a position probably forget that the value of a journal depends to a certain extent not only on the articles which are contributed to it but on the people who read it, and they probably forget also that only where there are sufficiently large numbers of readers does the average contributor of excellent articles wish to publish his contribution. The few advertisements which have been published in the JOURNAL have always been of high order and carefully scrutinized by the American Medical Association. It has published from time to time the transactions of the American Pediatric Society, of the American Society of Pediatric Research and of many of the local societies, notably those of New York, Philadelphia and Chicago. Withal, while it has been essentially a scientific journal, it has had to appeal to the higher type of practitioner of pediatrics. He has not had to go through the literature of several journals to be able to obtain the gist of pediatric thought in the world. It has always maintained, so far as I can determine, a very fair editorial judgment. Its Editorial Board has looked on the contributions without bias or favor. The members of the Board have usually been constructively critical and this without exception during the period that I have acted as its Chief Editor. All articles are submitted to at least two members of the Editorial Board, and these two members must not reside in the city from which the articles come. Every attempt has been made to judge every contribution on its merit, and rarely has an article appeared which has suffered criticism from the standpoint of scientific inadequacy. On the whole, the JOURNAL may be said to have become a leader in American and, therefore, world pediatrics, and it is to be hoped that down the years it may maintain the high standard which has been part of its being.

Case Reports

CLEIDOCRANIAL DYSOSTOSIS SYNDROME

Report of a Case in a Negro Child Exhibiting Retarded Growth

ROLAND B. SCOTT, M.D.
AND
L. OTTO BANKS, M.D.
WASHINGTON, D. C.

Cleidocranial dysostosis is a rare congenital syndrome which was originally described by Marie and Sainton [1] in 1897. According to the classic description, the syndrome consists in aplasia of one or both clavicles, exaggerated development of the transverse diameter of the cranium, delay in the ossification of the fontanels and hereditary transmission. At present the requirements for the diagnosis of the condition are less rigid than those originally set down by Marie and Sainton. Various workers [2] have reported atypical cases which did not fulfil the four requisites listed. To help to clear some of the confusion that surrounds this subject Fitchet [3] has suggested that use of the term "hereditary cleidocranial dysostosis" be discontinued and the condition be recognized for what it is, "a congenital cleidal dysostosis, either hereditary or nonhereditary, with or without other anomalies."

Clinically the most prominent sign is the defect of the clavicles and extreme mobility of the shoulder girdle. This sign can readily be elicited by the anterior proximation of the shoulders. Unilateral or bilateral, the defect usually consists in partial or total absence of the clavicles. The cranial part of the syndrome includes large open fontanels, bossing of the frontal, parietal and occipital bones, wide sutures, wormian bones, relatively small face and underdeveloped paranasal sinuses. The commonest associated defects are dwarfism, lordosis, prominence of thorax and abdomen, delayed dentition, coxa valga, coxa vara, absence of the various pelvic bones, imperfect long bones and short phalanges.

The cause of cleidocranial dysostosis is unkown, but the condition is considered to originate from a defect in the germ plasm.[4] The syndrome seems to occur in

---

From the Department of Pediatrics of Howard University School of Medicine and the Pediatric Service of Freedmen's Hospital.

1. Marie, P. S., and Sainton, P.: Observation d'hydrocéphalie héréditaire (père et fils), par vice de développement du crâne et du cerveau, Bull. et mém. Soc. méd. d. hôp. de Paris **14**:706, 1897.

2. Baer, R. W.: Congenital Cleidal Dysostosis, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 4, chap. 27. Fitzwilliams, D. C.: Hereditary Cranio-cleido Dysostosis, Lancet **2**:1466, 1910. Miles, P. W.: Cleidocranial Dysostosis: Survey of 6 New Cases and 126 from the Literature, J. Kansas M. Soc. **41**:462, 1940. Boland, M.: A Case of Rudimentary Clavicles, J. A. M. A. **58**:1442 (May 11) 1912. Cyriax, E.: A Case of Cleido-Cranio Dysostosis, Edinburgh M. J. **30**:600, 1923.

3. Fitchet, S. M.: Cleidocranial Dysostosis: Hereditary and Familial, J. Bone & Joint Surg. **11**:838, 1929.

4. (*a*) Cooper, L.: Cleidocranial Dysostosis: Report of a Case, M. Ann. District of Columbia **10**:334, 1941. (*b*) Fiese, M. J., and Flippen, J. H.: Hereditary Cleidocranial Dysostosis: Report of a Case. Stanford M. Bull. **3**:88, 1945.

all races.[5] We have been able to find only 3 cases [6] of its occurrence in American Negroes. The case reported here represents the fourth and is unique in that this 4 year old child has been followed since birth.

REPORT OF A CASE

L. S., a Negro girl, was born at Freedmen's Hospital on July 30, 1945, weighing 6 pounds and 14 ounces (3,100 Gm.). The 33 year old mother enjoyed excellent health throughout the pregnancy. The labor and delivery were reported as uneventful. On physical examination at the time of birth only the frontal and occipital bones could be palpated. There was a huge defect involving the vertex of the skull. Roentgen examination on the fourth day of life showed complete absence of the clavicles and all skull bones except the frontal and occipital. A

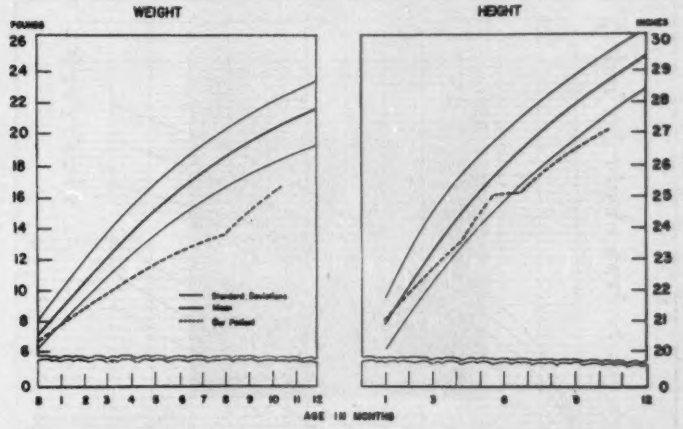


Fig. 1.—Retarded growth in weight and height of our patient for the first year of life compared with standards established from 654 normal Negro infants (Scott, R. B., Cardozo, W. W.; Smith, A. deG., and DeLilly, M. R.: Growth and Development of Negro Infants, to be published). The middle curve in the control series represents the mean weight and height, and the two extreme curves represent ± 1 standard deviation.

familial history of cleidocranial dysostosis was disclaimed. The infant was discharged six days after birth, and has been followed since that time by one of us (R. B. S.).

Certain aspects of the child's growth are presented in the table.

---

5. Lasker, G.: The Inheritance of Cleidocranial Dysostosis, Human Biol. **18**:103, 1946.

6. McCurdy, I. J., and Baer, R. W.: Hereditary Cleidocranial Dysostosis, J. A. M. A. **81**:9 (July 7) 1923. Krebs, O., and Terry, R. J.: Dysostosis Cleidocranialis, J. Missouri M. A. **19**:522, 1922.

Data on the Patient's Growth

Age, Mo.	Weight		Height, Inches	Head Circumference, Inches	Chest, Inches	Abdomen, Inches	Teeth
	Pounds	Ounces					
Birth	6	14	....	....	....	..	..
1	7	11	21	13⅜	13	12	..
2	8	10	21¾	14	13¼	..	..
4	10	8	23	14⅜	....	..	..
4½	11	..	23½	15	....	..	..
5½	12	..	25	15½	14¾	..	..
6⅜	12	13	25¼	15⅝	15½	..	..
7⅜	13	11	....	....	....	..	..
9	15	2	26½	16¾	....	..	..
10½	16	5	27	....	....	..	..
13⅜	18	2	28¼	17½	16½	..	8
26	21	8	32½	19	17½	16¼	..
52	27	..	36¾	19¾	18	..	20

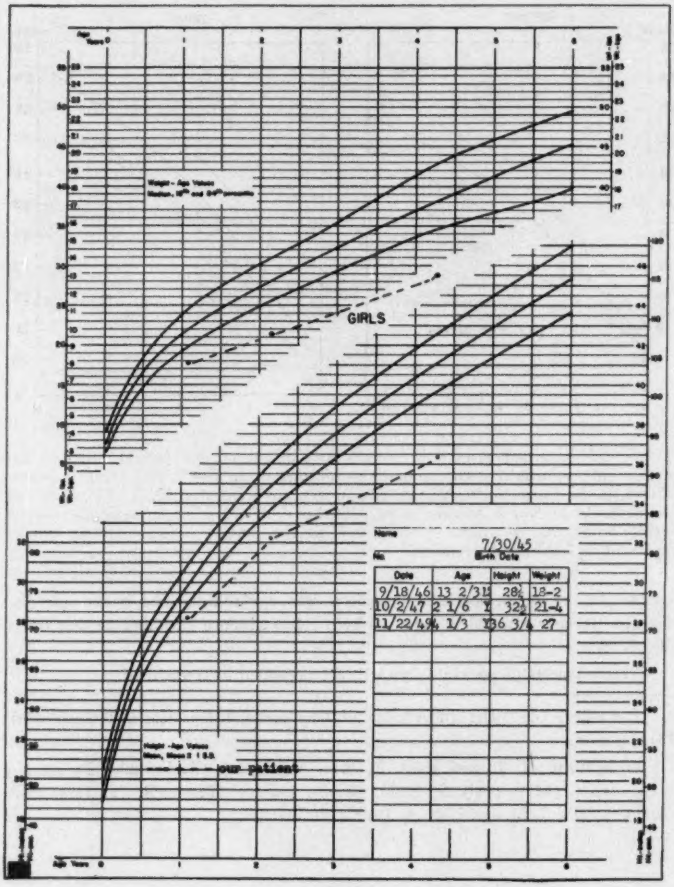


Fig. 2.—The retarded weight and height of the patient from 1 to 4 years is demonstrated by comparison with standards for this period compiled by the Iowa Child Welfare Research Station.

Fig. 3.—The patient at 4 years of age. Note the bossing of the forehead. Both shoulders are approximated anteriorly with ease. The lower extremities exhibit genu valgum and pes planus.

Fig. 4.—Roentgenogram of the chest taken four days after birth showing complete absence of the clavicles. The ossification centers at the proximal ends of the humeri are also absent.

The child's growth in height and weight, particularly the latter, was retarded during the first year of life (fig. 1). Growth continued at a subnormal level from the first through the fourth year (fig. 2).

The patient sat alone at 6 months. At 13 months the transverse diameters of the anterior and posterior fontanels were 5½ and 4 inches (14 and 10 cm.) respectively. A V-shaped hard palate and three teeth were noted at this examination. She could stand alone and walk with support. Speech was limited to monosyllables.

When the child was 26 months old, the fontanels were still widely patent; the anterior measured 5 by 4½ inches (13 by 11 cm.) and the posterior 2 by 2 inches

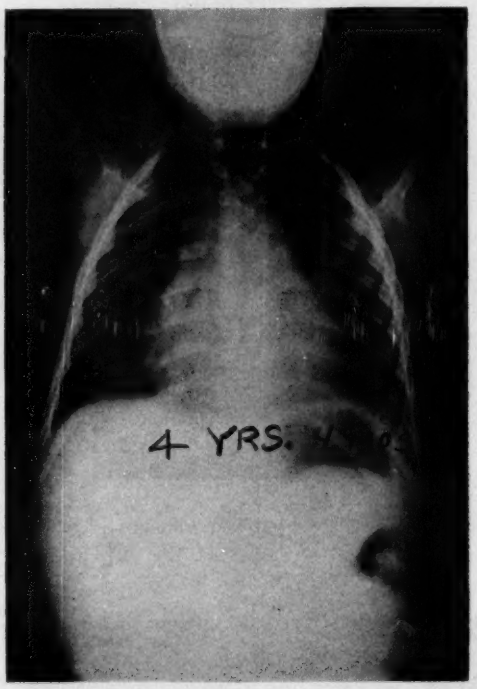


Fig. 5.—A posteroanterior view of the chest taken at 4½ years also reveals absence of the clavicles.

(5 by 5 cm.). The eyes appeared unusually prominent, and the interocular distance was exaggerated. There was malocclusion of the teeth. The shoulders were round and could easily be approximated anteriorly. Speech and gait were normal. The patient appeared small and malnourished at this time. She was seen again at the age of 4 years (fig. 3), presenting smallness of stature, genu valgum and pes planus. Her physical development was that of a 2 year old child. All twenty teeth were present. The anterior fontanel was still patent and measured 3 by 4½

inches (8 by 11 cm.). The posterior fontanel was closed. The child appeared alert and active. Speech was normal.

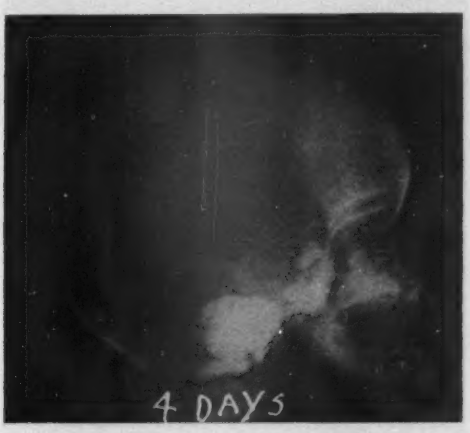


Fig. 6.—Roentgenogram of the skull of the infant at 4 days reveals only a shell of the frontal and occipital bones. Both parietal bones are entirely membranous in type and do not visualize on the roentgenogram.

Fig. 7.—Lateral view of the skull taken at 7 months shows greater calcification in the frontal and occipital bones. Many wormian bones are noted in the parietal regions where calcification is imperfect and creates a mosaic-like pattern.

Figures 4 to 10 are reproductions of periodic roentgenograms of the skeletal system from infancy to 4 years.

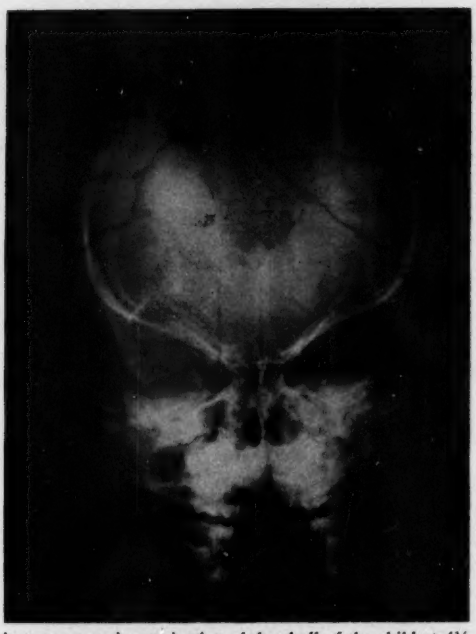


Fig. 8.—A posteroanterior projection of the skull of the child at 4⅓ years shows a large cranium with a wide transverse diameter, large patent anterior fontanel and wormian bones.

Fig. 9.—Roentgenogram of the pelvis at 4⅓ years revealing wide separation of the ilia and ischia and absence of the pubic bones.

COMMENT

Our patient presented the characteristics of the syndrome as originally described by Marie and Sainton, with the exception of the hereditary trait. When she was last examined, at the age of 4⅓ years, the anterior fontanel was still patent. Her weight, stature, dentition and epiphysial maturation were retarded throughout the four year period of observation. Periodic roentgenograms demonstrated typical findings of the syndrome, namely, total absence of the clavicles, faulty ossification of the cranium with patent fontanels and many wormian bones. Delayed bone age and absence of the pubic bones were additional significant findings.

Fig. 10.—Roentgenogram of the lower extremities taken at the age of 4 days revealing complete absence of the five centers (tibial and femoral at the knee; calcaneus, astragulus and cuboid at the ankle) usually present at birth.

The dwarfed stature, retarded dentition, delayed epiphysial maturation and faulty bone development of our patient were attributed to a widespread defect in the germ plasm which we believe is characteristic of the cleidocranial dysostosis syndrome. Other forms of dwarfism and retarded bone development such as cretinism, rickets and dyschondroplasia (chondrodystrophy) were ruled out by clinical and/or laboratory observations. Our patient was mentally alert and active at all times. Vitamin D intake was adequate, and rachitic changes were never observed in any of the serial roentgenograms.

It is unfortunate that the term "cleidocranial dysostosis" has caused the defects of the clavicle and the skull to be emphasized to the neglect of other portions of the body. Anspach and Huepel [7] have indicated that this is a widespread skeletal disease, and, indeed, Cooper [4a] has enumerated over one hundred abnormalities that have been associated with this syndrome.

SUMMARY

A case of cleidocranial dysostosis in a 4 year old Negro girl is reported. Physical growth and roentgenographic studies are recorded for the first four years of life. In addition to the typical cleidocranial defects, the child exhibited retarded physical, dental and epiphysial growth, as well as absence of the pubic bones. We attributed the defective skeletal and physical development to a widespread deficiency in the germ plasm which we believe to be part of the cleidocranial dysostosis syndrome.

7. Anspach, W. E., and Huepel, R. C.: Familial Cleidocranial Dysostosis (Cleidal Dysostosis): A Preosseous and Dentinal Dystrophy, Am. J. Dis. Child. **58**:786 (Oct.) 1939.

DERMATOMYOSITIS WITH NEPHRITIS IN A NEGRO GIRL

J. EDMUND BRADLEY, M.D.
MILES E. DRAKE, M.D.
AND
H. PATTERSON MACK, M.D.
BALTIMORE

Dermatomyositis, a rare subacute or chronic disease of protean clinical and pathologic manifestations, was first described in 1863.[1] The disease is characterized by erythematous skin eruptions, edema of the skin and subcutaneous tissues, muscle pain and degeneration of many of the muscles of the body, together with a nonsuppurative inflammation of the skin and mucous membranes. There may be biochemical alterations, especially in the albumin-globulin and in the urinary creatine-creatinine ratios. While the disease is commonest in middle-aged persons, approximately 15 per cent of the patients are children. As late as 1944[2] it was stated that the disease affects only members of the white race. However, Irgang[3] described 2 cases of its occurrence in Negroes, but to our knowledge there have been no reports of cases in Negro children.

REPORT OF A CASE

E. C., a 7 year old Negro girl, was admitted to the pediatric service of the University Hospital on July 8, 1948, with a chief complaint of extreme weakness, loss of weight and pains in the muscles of the legs and arms on active and passive motion and on palpation. There was a rash of two months' duration. The child had been well until May 1948, when she was seen in the skin clinic because of an erythematous, edematous rash on her face. The impression was that she had erythema multiforme, and starch baths for the face twice daily were prescribed. This seemed to aggravate the condition, and the mother discontinued the treatment and did not return. The rash persisted, with extension to the neck, body and extremities. The child became progressively weaker; painful muscles and hoarseness developed. Her appetite remained good.

There was no history of antecedent infection or illness and no pica. The family history was noncontributory. Significant conditions noted at the time of admission were a temperature of 37.5 C. (99.5 F.) (rectal); a pulse rate of 94 a minute, and a blood pressure of 100/80, which increased to 120/100 prior to death. The patient weighed 15 Kg. and was obviously malnourished. She was an acutely ill child with a brawny hard edema of the legs, arms and face. The skin of the face, arms, legs and body was covered with dull red, annular, macular, serpiginous, scaling lesions which measured 0.5 to 3 cm. in diameter. Many of the lesions showed

Department of Pediatrics, University Hospital and University of Maryland School of Medicine.

1. Wagner, E.: Fall einer selten Muskelkrankheit, Arch. d. Heilk. **4**:282, 1863.

2. Lamb, J. H.: Dermatomyositis, J. Oklahoma M. A. **37**:5, 1944.

3. Irgang, S.: Dermatomyositis in the Negro: A Clinical and Histological Study of the Skin of 2 Cases, Urol. & Cutan. Rev. **46**:251, 1942.

atrophic scarring and depigmentation. The hair was scanty, and the eyelashes were long. The muscles of the arms and legs were moderately atrophic, with extreme tenderness on passive and active motion and on palpation. The child's face was the most striking feature. There was a brawny edema of the malar regions with a rosy tinge to the edematous eyelids; closer inspection revealed the rosy tinge to be due to many small telangiectases. The net effect was a heliotrope bloating of the face, resembling the early stages of cadaveric decomposition. The teeth were carious, and the mucous membranes had lesions similar to those described on the skin. Ophthalmoscopic examination revealed a fluffy exudate about the vessels. The lesions were not well circumscribed and tended to fade into the normal retina. The disks were normal. The lungs were clear on percussion, but on auscultation there were fine inspiratory and expiratory rales at the base of each lung posteriorly. The heart was not enlarged, and there were no murmurs. During the patient's hospital course her heart progressively enlarged with the development of a blowing systolic murmur at the mitral region. The spleen was palpable to 1½ fingerbreadths below the costal margin. Laboratory study showed 6.0 Gm. of hemoglobin per 100 cc., 2,760,000 erythrocytes and 15,850 leukocytes, with a differential count of 85 per cent segmented cells; 10 per cent lymphocytes; 1 per cent monocytes, and 3 per cent eosinophils. The thrombocyte (platelet) count was 313,000. This varied but slightly during her stay in the hospital, in spite of repeated whole blood transfusions and penicillin therapy. The sedimentation rate was corrected to 0. The urine on admission was acid with a specific gravity of 1.012, and albumin (2+) but no casts or red or white blood cells. There was a progressive increase in the excretion of albumin (to 4+) in the urine with the appearance of casts of all types and a few red and white blood cells. The specific gravity remained between 1.012 and 1.028. The tuberculin test elicited a negative reaction in dilutions of 1:1,000 and 1:100. The reaction to a serologic test for syphilis was negative, and repeated blood cultures and gastric washings were negative. The blood urea nitrogen was 26 mg. per 100 cc., which rose to 56 mg. per 100 cc. prior to death. The blood sugar (glucose) was 61 mg. per 100 cc., the serum chlorides, 72 milliequivalents and the carbon dioxide content 28 milliequivalents per liter. The total blood proteins were 5.08 Gm. per 100 cc., with an albumin-globulin ratio of 4.05:1.03. The total proteins were altered little during the patient's course in the hospital, but there was a marked albumin-globulin ratio reversal to 1.96:3.37. Nasopharyngeal cultures grew out Diplococcus pneumoniae and a streptococcus of the viridans group. Lumbar puncture yielded fluid under normal pressure, with normal cell count and chemical composition which was sterile on culture and guinea pig inoculations. The daily urinary excretions of creatinine and creatine respectively were 1.75 to 2.0 Gm. and 0.43 to 1.0 Gm. The peripheral insulin reaction showed the arterial and venous levels to be almost equal. The initial roentgenogram revealed no abnormalities, but repeated roentgenograms showed increasing pneumonitis of the bases of both lungs and progressive cardiac enlargement with effusion. Electrocardiograms revealed low voltage in T waves and QRS complexes in limb leads, which was suggestive of myocardial damage. Biopsy of the skin was indicative of chronic inflammation. Biopsy of the gastrocnemius muscle revealed atrophic changes with loss of striation plus lymphocyte and plasma cell infiltration. The rectal temperature rose to 40.5 C. (104.9 F.) and the pulse rate to 160 to 180. The child failed to respond to oxygen and antibiotic therapy. The administration of paraaminobenzoic acid in 2 Gm. doses every two hours and histamine hypodesensitization were without effect. The lead in the blood was reported as 0.03 mg. per 100 cc. Intractable pulmonary edema

developed and was followed by cerebral edema. The patient lapsed into coma, had frequent convulsions and died on her sixty-fourth hospital day.

Necropsy.—The significant observations in postmortem examination noted were a well developed, undernourished, cachetic Negro girl who showed marked atrophy of all the voluntary muscles, anasarca, partial alopecia of the scalp and generalized scattered lesions of the skin.

On opening the thorax considerable difficulty was encountered in raising the sternum from the mediastinum. There were generalized spider-web adhesions scattered over both pleural surfaces, and these sealed the lungs firmly to the chest wall. The heart was obviously enlarged; the transverse diameter of the thorax was 18 cm., and that of the heart 11 cm. When the pericardium was opened, the visceral and parietal surfaces were rather firmly adherent along the anterior wall of the heart near the apex. These adhesions were less marked as the base was approached. After the pericardium was stripped off the heart, the typical bread and butter appearance was noted.

Heart: The epicardial surface was shaggy with fibrinous exudate and was multicolored because of a varying degree of erythema. The pulmonary artery was opened and carefully inspected for an embolus; none was seen. The heart weighed 230 Gm. unopened. The tricuspid valve measured 8 cm.; mitral, 7 cm.; pulmonic, 6 cm., and aortic, 4.5 cm. The left ventricular wall was 1.3 cm. and the right ventricular wall 0.8 cm. in thickness. The endocardial surface was smooth and devoid of pathologic change. All the valves were well formed and delicate.

Kidneys: The left kidney weighed 150 Gm. and the right 180 Gm. The two kidneys were similar in appearance. On section the straight vessels of the cortex were seen to be dilated, and the pyramids were swollen and yellowish. The cortex was dark. The capsule stripped easily, leaving a smooth surface. The pelves and ureters were of normal caliber, and the bladder was not remarkable. There were no erosions, thickenings or vegetations of any of the valves. The myocardial tonus was good, and the muscle was of an average normal color. There were no areas of hemorrhage, infarction or atrophy.

Lungs: The right lung weighed 230 Gm. and the left 290 Gm. The pleural surfaces were covered by scattered fibrinous exudate, and in the lower lobe of the right lung posteriorly there was a thickened milky area approximately 3 cm. in diameter; there the lung was quite adherent to the thoracic wall. The pleural surfaces of both lungs were thickened; this was especially marked in the lower lobe of the right lung. The cut surface of each lung revealed slight edema and congestion; this was more marked in the posterior region of the right lung. The interlobar fissures were filled with delicate adhesions.

Microscopic Notes: The epicardial surface was covered by a layer of fibrin deposit. The endocardium was devoid of significant pathologic changes. A few minor areas of focal ischemic necrosis and leukocyte infiltration were noted in the myocardium. Many scattered myocardial fibers were curled and broken and stained more densely than the normal adjacent fibers. There was no loss of cross striation of the abnormal fibers, and no associated fibrosis or acute inflammatory reaction was seen. One section displayed an obvious increase in the number of nuclei associated with abnormal myocardial fibers. Most of these nuclei seemed to belong to monocytic cells, and some probably originated from the myocardial fibers.

Sections taken from the area of pleural thickening in the lower lobe of the right lung showed parenchymal congestion and edema with early bronchopneumonia. The pleura and its subjacent layers were edematous and covered by a layer of fibrin deposit which had undergone early organization and contained a few scattered areas of acute necrosis.

Most glomeruli had undergone some hyalinization. Many tufts exhibited hyalin fibrosis only near the vascular root, and the remainder of the glomerulus appeared normal. Other glomeruli were almost completely obliterated by hyalinization and droplet degeneration. A few were seen which contained crescents of hyperplastic cells originating from the capsule. The epithelial linings of some proximal and distal tubules had undergone droplet degeneration. Dense eosinophilic plugs were noted in many distal and collecting tubules.

In the skin there was flattening of the basal layer and thinning of the prickle cell layer. One lesion displayed edema of the superficial dermal layers and tips of the rete pegs. Mild acute and chronic inflammatory reactions with minimal fibrosis and atrophy were noted in the superficial dermal strata.

Muscle tissue taken from the intercostal, pectoral, diaphragm and extraocular muscles all exhibited, to a greater or less degree, the same pathologic changes noted in the myocardium. Scattered fibers were curled, broken and swollen and varied in staining quality. The cross striations were well demonstrated by Masson's technic but in most cases were scarcely perceptible with hematoxylin and eosin stain. The section of extraocular muscle showed an increase in the number of nuclei along one border. Most of the nuclei seemed to belong to monocytes, but others appeared to arise from muscle cells. One abnormal fiber showed several nuclei grouped together in a small clump. There was no acute inflammatory reaction associated with the abnormal muscle fibers.

COMMENT

The case reported is of special interest, first, because the disease occurred in a Negro child; second, because it was complicated by severe nephritis and retinal changes and, third, because it was complicated by brain changes, which will be reported in a subsequent publication.

There are certain similarities in the pathology of systemic lupus erythematosus, periarteritis nodosa, scleroderma, rheumatoid arthritis, verrucous endocarditis, calcinosis universalis, thromboangiitis obliterans and dermatomyositis and in the normal aging process. The "accelerated aging"[4] process of the vessels, primarily, and of the collagenous tissues, secondarily, may well be the basis of the pathogenesis of the so-called diffuse vascular or collagen diseases. The similarity between the vessels in chronic scleroderma and those in arteriosclerosis of old age is striking. Furthermore, thromboangiitis obliterans is a well defined clinical entity, and it is only recently that the diffuse vascular complications, with their concomitant damage to viscera, have been recognized. It is undoubtedly true that the vascular damage precedes and is responsible for the visceral and peripheral symptoms. The comparison with the aging process becomes evident only when the vessel affected by healed thromboangiitis obliterans with fibrosis, hyalinization and compromise of the lumen is compared with the usual arteriosclerotic process.

The comparison with periarteritis nodosa is more difficult, but careful searching will show vessels that resemble the aging process.

In disseminated lupus erythematosus the vascular lesions are generally limited to arterioles and capillaries. The clinical lesions of lupus erythematosus can easily be explained by diffuse vascular lesions, as shown by the "wire loop" capillaries in the glomeruli, and the cutaneous lesions likewise are predominantly vascular.

---

4. Yardumian, K., and Kleinerman, J.: Pathogenesis of So-Called Diffuse Vascular or Collagen Disease, Arch. Int. Med. **83**:1 (Jan.) 1949.

Dermatomyositis has much in common with scleroderma and calcinosis universalis, and there are many striking resemblances, especially in those cases with renal and retinal involvement, to disseminated lupus erythematosus. The vascular changes in dermatomyositis are less pronounced than in lupus erythematosus and scleroderma, but careful examination of biopsy and postmortem specimens showed many arterioles with the thickening of the walls and hyalin and collagenous degeneration. The renal involvement is less frequently encountered in dermatomyositis than in disseminated lupus erythematosus; however, when present it presents the same microscopic picture, namely, glomerular hyalinization with many tufts exhibiting only hyaline fibrosis near the vascular root. All these changes in the collagen diseases are comparable and compatible with the aging process as seen in many instances in life. Yardumian and Kleinerman,[4] in a recent article, presented the "accelerated aging process" as a basic cause for the vascular changes with resulting secondary collagen changes which may give rise to any of the aforementioned diseases but which we believe are all of a common pathogenesis.

It is well known that the medium-sized arteries and arterioles of the uterus and ovaries show advanced hyalinization of the media and intima. These changes are out of all proportion to the age of the person from whom the organs have been removed and furthermore are absolutely unrelated to the condition of vessels elsewhere in the body.

It would seem to us that there is considerable correlation between the pathogenesis of the aforementioned diseases and the normal aging process in that the pathologic change is predominantly in medium-sized vessels. It is not our opinion that these diseases have a single etiologic factor; on the contrary, we feel they have a multiplicity of causative agents, toxic in nature and all working in unison to give rise to an "accelerated aging process." Thus we believe lupus erythematosus disseminatus and dermatomyositis may be but manifestations of the same basic pathologic process, namely, involvement of the medium-sized arteries and arterioles.

SUMMARY

A case of dermatomyositis in a Negro girl is presented. The similarity of dermatomyositis and lupus erythematosus disseminatus is discussed.

Progress in Pediatrics

MIXED TUMOR OF THE LIVER

Report of a Case with a Review of the Literature

DORIS H. MILMAN, M.D.
AND
DAVID M. GRAYZEL, M.D., Ph.D.
BROOKLYN

AMONG primary tumors of the liver, the group classified as mixed or embryonal is least common and least well recognized as a pathological entity. A search of the literature up to 1949 reveals only 26 such cases, two of which have been reported in this country. Nissel [1] reviewed the German literature in 1928 and found 12 cases. Sheehan [2] collected nine cases in 1930, two of which had not been included in Nissel's series. Hartz and van der Sar,[3] in describing their case in 1945, commented that they could find no similar case in the literature and cited a personal communication from Edith L. Potter to confirm their impression. It is considered pertinent, therefore, to report the present case and to summarize the literature to date.

REPORT OF CASE

First Hospital Admission.—O. E., a 6 year old white boy, was admitted to the Jewish Hospital of Brooklyn for the first time on April 16, 1946 because of an enlarged abdomen and increasing fatigability. The child's illness had first been noted at the age of 20 months, when it was observed that he was losing weight and that his abdomen was unusually large, whereas his extremities were thin and spindly. The size of the abdomen varied in the course of a day, being considerably larger in the evening than in the morning. The mother recalled that it had been necessary to provide him with different sized clothing to wear at different times during the day. After hospitalization at the age of 26 months the child was considered to have an enlarged liver of unknown cause. He was treated with a diet high in carbohydrate and supplemented with vitamins. He grew and gained weight slowly. His abdomen continued to enlarge out of proportion to his skeletal growth but no longer showed any diurnal variation in size. On Feb. 26, 1946 he was readmitted to one of the hospitals at which he had previously been studied. Again an enlarged liver was found, and a glucose absorption study showed no rise in blood sugar. For this reason he was thought to have von Gierckе's disease (glycogenosis), and he was discharged on a restricted dietary regimen. He was admitted to the Jewish Hospital of Brooklyn one month later for further study.

The patient was a thin undersized chronically malnourished child. His weight was 46 pounds (21 Kg.). He was pale and sallow, except for bright red lips and ear lobes. Examination of the eyes, ears, nose, throat and lungs revealed no abnormalities. The heart seemed to be somewhat enlarged to the left, with the point of maximum intensity in the fifth left intercostal space 2 cm. lateral to the nipple line. The heart sounds were of normal quality,

From the Departments of Pediatrics and Laboratories of the Jewish Hospital of Brooklyn.

1. Nissel, W.: Die Mischgeschwülste der Leber, Virchows Arch. f. path. Anat. **269**: 446, 1928.

2. Sheehan, H. L.: Embryonic Tumor of Liver Containing Striated Muscle, J. Path. & Bact. **33**:251, 1930.

3. Hartz, P. H., and van der Sar, A.: Teratoma of the Liver in an Infant, Am. J. Clin. Path. **15**:159, 1945.

and the rhythm was rapid and regular. A systolic blowing murmur was heard in the third left intercostal space at the sternal margin. The systolic blood pressure was 156 mm. and the diastolic 114 mm. The abdomen was grossly enlarged, and many veins were visible over the abdominal and chest walls. A mass was seen to occupy the entire right side of the abdomen (fig. 1). On palpation the mass was found to be firm, smooth and nontender. It was ovoid in shape and extended from the costal margin to the iliac crest and from the midline laterally into the right flank. It did not appear to move with respiration. Partially

Fig. 1.—Lateral view of child preoperatively, showing the abdominal mass and dilated veins over the chest wall, abdomen and upper thighs.

overlying this mass and easily distinguished from it was another mass that was considered to be liver, since its border was parallel to, and 3 fingerbreadths below, the right costal margin. The latter mass was smooth and firm, had a sharp edge and moved with respiration.

Examination of the urine showed nothing abnormal. The hemoglobin concentration was 88 per cent, and there were 4,440,000 red blood cells per cubic millimeter. There were 9,200 leukocytes per cubic millimeter, of which 47 per cent were polymorphonuclear neutrophils, 4 per cent eosinophils, 1 per cent basophils, 40 per cent lymphocytes and 8 per cent monocytes.

A Kline test of the blood showed negative results. The erythrocyte sedimentation rate was 56 mm. in one hour by the Westergren method. The urea nitrogen level in the blood was 16.7 mg. per 100 cc. The carbon dioxide-combining power was 59.2 volumes per 100 cc. Evaluation of hepatic function was based on the following chemical determinations: The total protein was 6.55 Gm. per 100 cc.; the albumin, 3.65 Gm., and the globulin, 2.90 Gm. The ratio of albumin to globulin was 1:2. A cephalin-cholesterol flocculation test gave a negative reaction. A thymol turbidity determination was positive up to 1.6 units. The prothrombin time measured 9.5 seconds, as compared with a control of 12.6 seconds. The level of phosphorus in the blood was 4.1 mg. per 100 cc., and the alkaline phosphatase was 5.1 units per 100 cc. A glucose absorption study done on venous blood gave the following results: The fasting blood level was 63 mg. per 100 cc.; one hour after the ingestion of 37 Gm. of glucose, the level was 87 mg.; two hours later, 76 mg., and three hours later, 93 mg.

An electrocardiogram showed deviation of the electrical axis to the right, notching of the P wave in lead I and a P-R interval of 0.16 second, with a ventricular rate of 135. When the ventricular rate fell to 90 a minute, the P-R interval was found to be 0.20 second.

A roentgenogram of the chest showed slight elevation of the right leaf of the diaphragm. The heart shadow was considered to be normal. The lung fields likewise were normal. Roentgenograms of the skeletal system revealed nothing abnormal. A plain roentgenogram of the abdomen showed a large shadow on the right, its lower border being at the level of the iliac crest. On an excretory urogram both kidneys were well outlined. The left kidney appeared entirely normal. The pelvis of the right kidney filled poorly and was distorted and elongated in its lower pole.

The clinical diagnosis was somewhat in doubt, a diagnosis of Wilms's tumor (embryonal carcinosarcoma) or other retroperitoneal neoplasm being held most likely. The elevation in blood pressure suggested the possibility of a pheochromocytoma. Because it was thought that an exact diagnosis could be arrived at by surgical exploration, a laparotomy was performed on April 26, 1946. The abdomen was opened through an oblique incision which paralleled the right costal margin. A large globular tumor, measuring about 8 inches (20 cm.) in diameter, was encountered arising from the under surface of the right lobe of the liver and occupying about ¼ to ⅓ of the abdominal cavity. The intestines were pushed into the pelvis and over to the left side of the abdomen. The right lobe of the liver was compressed and flattened by the tumor. The liver itself was not appreciably enlarged. The right kidney appeared normal in size, shape and location. There were fibrous adhesions between the tumor and the adjacent duodenum and right side of the colon. Large blood vessels coursed down from the right lobe of the liver onto the tumor. After a plane of cleavage from the under surface of the liver had been established, the entire tumor was removed intact. A small portion of the lateral aspect of the right lobe of the liver was removed with the tumor. The postoperative course was complicated by the development of atelectasis of the upper lobe of the right lung, which resolved spontaneously after three days.

Studies of the blood postoperatively showed normal values for serum protein, serum albumin and globulin, cephalin flocculation, thymol turbidity, prothrombin time and cholesterol. A glucose tolerance test repeated 18 days after operation showed a normal configuration, with a fasting level of 121 mg. per 100 cc. of blood, a rise to 160 mg. in ½ hour and a fall to 115 mg. in three hours. An electrocardiogram taken after operation showed that there was still right deviation of the electrical axis. The P-R interval was 0.14 second, with a heart rate of 135 a minute. The blood pressure postoperatively was considerably lower, the systolic varying between 124 mm. and 108 mm., the diastolic between 80 mm. and 64 mm.

Pathological Observations.—The specimen (figs. 2 and 3) consisted of a large spherical mass 17 by 14 by 6.6 cm. with a small portion of attached liver tissue. The latter was mottled yellow and green and was moderately firm. The tumor was well encapsulated and soft, and its external surface was smooth and glistening. The cut surfaces were lobulated, varied in color from gray to pink and red-brown and contained numerous hemorrhagic areas.

Histologically, the tumor was encapsulated by dense collagenous fibrous tissue. It was fairly well vascularized and showed scattered foci of necrosis. The tumor cells were of three

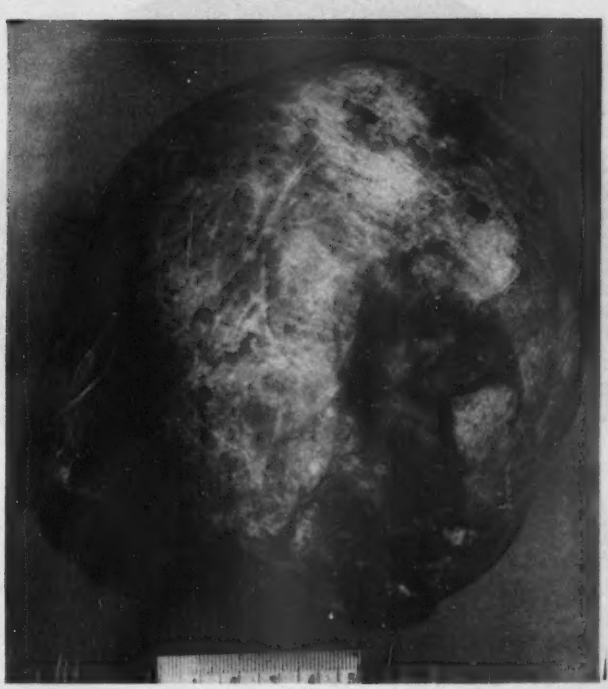


Fig. 2.—Tumor removed at operation.

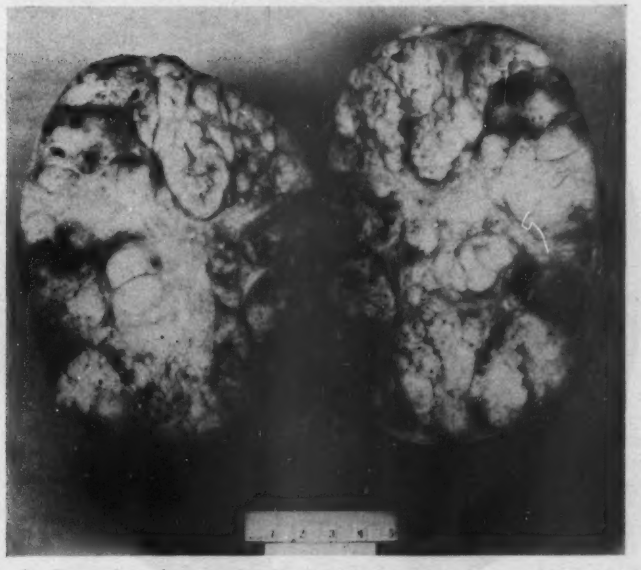


Fig. 3.—Cut surface of tumor, showing lobulated nature and areas of hemorrhage.

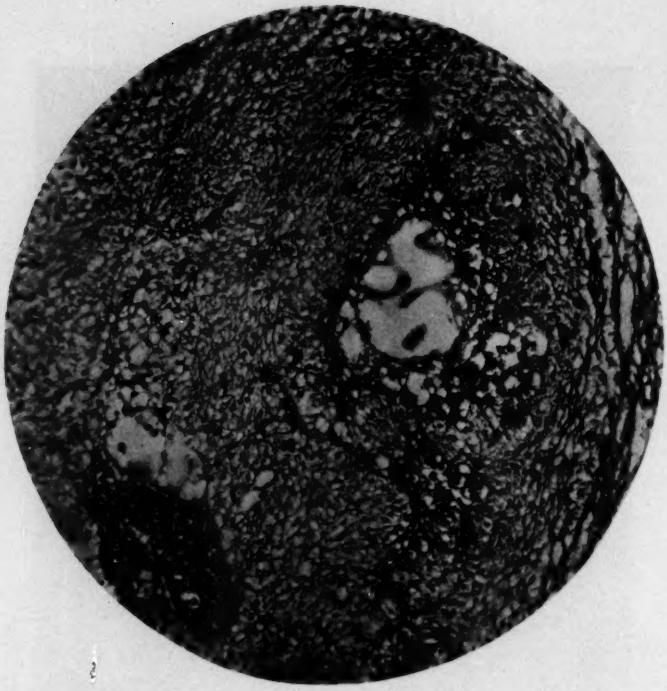


Fig. 4.—Tumor tissue, showing islands or cords of large polygonal cells in a loose myxomatous stroma. Hematoxylin and eosin stain; × 120.

Fig. 5.—Tumor tissue, showing the different types of epithelial cells arranged in cords, nests and rudimentary ducts. Hematoxylin and eosin stain; × 300.

well defined types. One consisted of fairly large polygonal cells with well defined cell borders, abundant granular eosinophilic cytoplasm and round, deeply staining nuclei (fig. 4). These cells were arranged in cords or masses and resembled liver cells. The second type consisted of smaller cells with round or ovoid vesicular nuclei and scanty clear or slightly basophilic cytoplasm. These were arranged in alveolar configurations. In places, however, there were pseudorosette formations or small rudimentary ductlike structures. The third type consisted of cells with relatively small nuclei and fairly abundant pale or clear cytoplasm. These cells formed variously sized nests. The different cell groups intermingled in places (fig. 5). Mitotic figures were numerous, and there was invasion of venules (fig. 6). The stroma in some areas was of a loose myxomatous nature (fig. 4) and in other areas consisted of bands

Fig. 6.—Section through a venule, showing the presence of tumor thrombi. Hematoxylin and eosin stain; × 80.

of dense collagenous fibrous tissue. The anatomic diagnosis was mixed embryonal tumor of liver (malignant).

Follow-Up Examination.—On Dec. 30, 1946, nine months after operation, the boy was apparently well. He weighed 49 pounds (22 Kg.), a gain of 6 pounds (3 Kg.) over his weight on discharge from the hospital. His blood pressure was 104 mm. systolic, 70 mm. diastolic. The heart sounds were of normal quality, and no murmurs were heard. The abdominal wound was well healed. The liver edge could be palpated just below the costal margin on deep inspiration. It was smooth, regular, firm and nontender. An electrocardiogram showed no deviation of the electrical axis, regular sinus rhythm with a rate of 94, P-R interval of 0.16 second, notched P waves in leads I and II and inversion of the P wave in lead III. A roentgenogram of the chest showed clear lung fields and a normal cardiac silhouette.

Second Hospital Admission.—On routine examination a roentgenogram of the chest taken on April 24, 1947 showed many small round opacities in both lung fields, characteristic of metastatic tumor growth. For that reason the child was readmitted to the hospital on May 5. During the 10 month period after the first hospital admission the child seemed well, gained 10 pounds (5 Kg.) in weight and attended school. His only complaint was unusual fatigability.

The child was well nourished and did not appear ill. Several small firm axillary, cervical and inguinal lymph nodes were palpable. His abdominal scar was well healed. The liver edge could not be felt. Auscultation of the thorax revealed nothing unusual.

Examination of the urine revealed no abnormalities. The hemoglobin concentration was 100 per cent, and there were 5,350,000 red blood cells per cubic millimeter. The white blood cells numbered 9,500 per cubic millimeter, of which 44 per cent were polymorphonuclear neutrophils, 54 per cent lymphocytes and 2 per cent monocytes. The erythrocyte sedimentation rate was 11 mm. in one hour by the Westergren method. Chemical examination of the blood revealed the following values: phosphorus, 4.8 mg. per 100 cc.; phosphatase, 3.5 Bodansky units; total protein, 7.62 Gm.; albumin, 5.07 Gm.; globulin, 2.55 Gm.; total cholesterol, 194 mg., and free cholesterol, 47.3 mg. Roentgenograms of the bones showed no evidence of metastatic disease.

The child received a course of Coley's toxin, intravenously at two day intervals for a total of seven injections. He was discharged on May 27 after 23 days in the hospital, his condition essentially unchanged.

Third Hospital Admission.—For the next 11 months the child appeared to improve and gained 20 pounds (9 Kg.) in weight. In May 1948 the child experienced a transient frontal headache. Thereafter, headaches recurred at increasingly frequent intervals and were accompanied with vomiting. In October 1948 increasing weakness of the right arm and leg and the right side of the face were noted.

On readmission to the hospital on October 23 he appeared chronically ill and emaciated. He was unable to sit even with support. There was a right hemiparesis involving the face, arm and leg. The deep tendon reflexes on the right side were hyperactive and the Babinski reaction was positive. Visual acuity was markedly diminished, and the optic disk margins were blurred. Examination of the chest revealed dulness over the left hemothorax and diminished breath sounds over both lung fields. The liver edge was felt 2 cm. below the costal margin. The systolic blood pressure was 90 mm. and the diastolic 65 mm.

The hemoglobin concentration was 80 per cent, and there were 4,840,000 red blood cells per cubic millimeter. The white blood cells numbered 12,650 per cubic millimeter, of which 60 per cent were polymorphonuclear neutrophils, 41 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. The erythrocyte sedimentation rate was 55 mm. in one hour. Chemical examination of the blood revealed the following values: calcium, 9.5 mg. per 100 cc.; phosphorus, 4.6 mg.; phosphatase, 3.3 Bodansky units; total cholesterol, 221 mg.; free cholesterol, 69.3 mg. (31.3 per cent); total protein, 6.7 Gm.; albumin, 4.1 Gm., and globulin, 2.6 Gm. Roentgen examination showed metastatic tumor deposits in the lungs. The bones appeared normal roentgenologically.

The child followed an unremitting downhill course, with progressively increasing paralysis and dyspnea; he died on Nov. 5, 1948. The death had occurred 6½ years after the illness was first noted and 31 months after removal of the tumor.

Postmortem Examination.—At autopsy the body was that of a thin white child 140 cm. long and 35 Kg. in weight. The liver weighed 870 Gm. The surface was red-brown and glistening, except at the site of the previous operation, where it was adherent to the hepatic flexure of the colon by dense fibrous adhesions. The right lung weighed 200 Gm. and the left 175 Gm. The bronchi were dilated and could be traced to the periphery. Within all the lobes there were rounded masses of moderately soft, gray-white tumor tissue (fig. 7). The left lung was more diffusely involved by tumor than the right. The tracheobronchial and mediastinal lymph nodes were enlarged, measuring up to 5 cm. in diameter, and when sectioned were found to be almost completely replaced by tumor. Moreover, tumor thrombi were present in the pulmonary veins extending into the right atrium of the heart. The brain weighed 1,650 Gm. The convolutions over the left hemisphere were flattened, and there was a large bulge in the left frontoparietal area. There was also a herniation of the left cingulate gyrus beneath the tentorium cerebelli. Coronal sections (fig. 8) of the brain

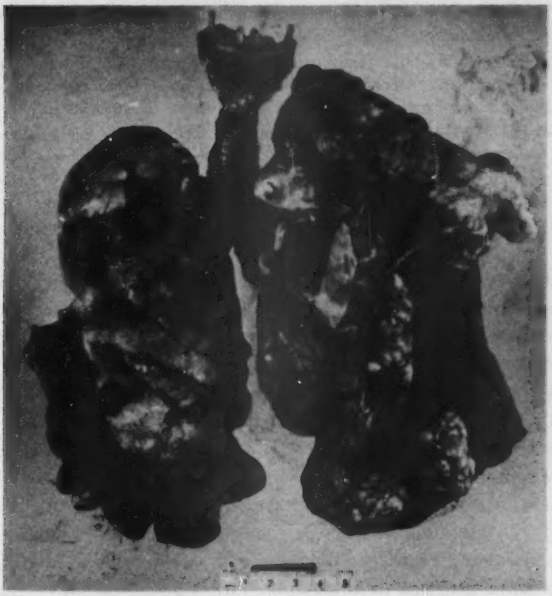


Fig. 7.—Lungs at necropsy, showing replacement of parenchyma by tumor masses.

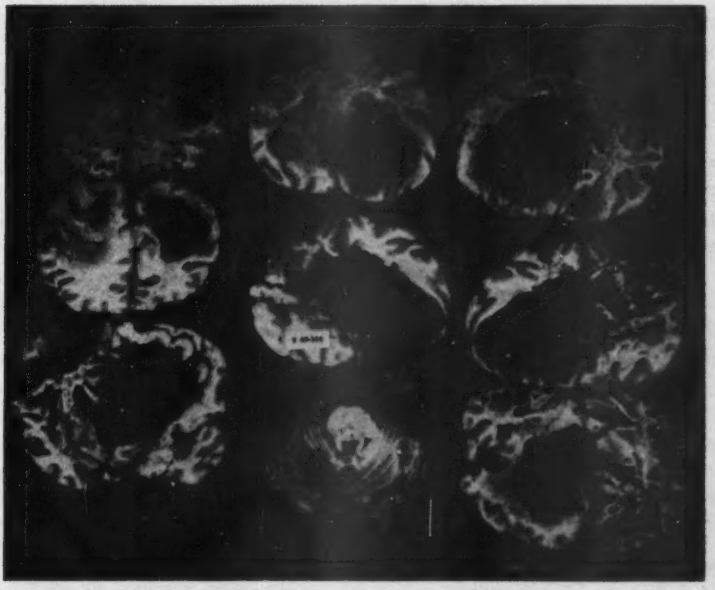


Fig. 8.—Coronal sections of brain, showing a large metastatic tumor in the left cerebral hemisphere and a smaller one on the right. Hemorrhage is evident within the masses.

revealed a large metastatic tumor mass 6 cm. in diameter in the left frontoparietal area and another mass 4 cm. in diameter in the right parieto-occipital area.

Microscopic examination of the tumor tissue of the lungs and brain showed the cytoarchitecture to be identical with that of the original tumor removed at operation. Examination of multiple sections of the liver failed to reveal the presence of tumor tissue.

The anatomical diagnoses were healed wound of operation for malignant mixed tumor (teratoma) of liver; metastases in mediastinal and tracheobronchial lymph nodes, lungs and brain; tumor thrombi in pulmonary veins; dilatation of heart; congestion of viscera; Meckel's diverticulum, and cortical adenoma in right adrenal gland.

COMMENT

Data with respect to the 27 cases of mixed tumor of the liver are summarized in the table. It will be seen that 18 of these, or 67 per cent, were of children, all of whom were less than 8 years of age. Nine of them were under 1 year of age. Nine cases, or 33 per cent, were of adults between 20 and 80 years of age. Fifteen patients were male and 10 were female, and in two instances the sex was not recorded.

The tumors were grouped together as a pathological entity because they all contained elements from more than one primary germ layer. Most of them contained epithelial tissue with a varying tendency toward adenomatous or acinar arrangement. In addition, connective tissue, sometimes of a highly embryonic myxomatous character, played a prominent role in the cellular composition of the tumor. In many instances differentiation into a more definitive type of tissue had taken place. In 19 cases the presence of bone or muscle or cartilage was observed. In many instances all types of connective tissue from the most primitive to the most highly specialized were represented. Likewise, the degree of differentiation of epithelial and endothelial elements was variable. Instances of all stages from the most embryonic and primitive, as in the present case, to the most adult type of differentiation were found.

The question of the etiology of embryonal tumors is still unanswered. The absence of cirrhosis in all cases suggests that the etiology is altogether unrelated to that of primary hepatoma, since the latter is so frequently found in association with portal cirrhosis. The earlier German pathologists (Hippel [4]) ascribed these tumor formations to the presence of multipotent embryonal cell rests in the liver or, less specifically, to a disturbance in the primary liver anlage. Sheehan [2] elaborated this concept to explain the heterotopic nature of the cellular constituents. He believed that not only the parenchymal rest cell type but also the primitive mesothelial or mesenchymatous cell participated in the tumor formation. He held that the more primitive the rest cell type the greater were its potentialities for tumor formation and cellular differentiation. Leffers [5] suggested the possibility that this type of tumor was a form of congenital carcinoma, with reversion of the malignant cells to a more embryonal form. Leffers also speculated as to whether the tumor arose from a single germ layer with subsequent differ-

4. Hippel, B.: Zur Kenntnis der Mischgeschwülste der Leber, Virchows Arch. f. path. Anat. **201**:326, 1910.

5. Leffers, I.: Über eine seltene, maligne Mischgeschwulst der Leber bei einem 16 Monate alten Knaben, Beitr. z. path. Anat. u. z. allg. Path. **105**:203, 1941.

Summary of Data on Twenty-Seven Cases of Mixed Tumor of the Liver

Case No.	Author	Year	Age	Sex	Duration of Symptoms	Treatment	Outcome	Tumor, Gross Characteristics	Histological Elements	Presence of Metastases	Malignancy	Author's Diagnosis
1	Walter, M.: Arch. f. klin. Chir. **53**: 1, 1896	1896	76 yr.	M	.....*	..*	Died	Multinodular	Epithelium, connective tissue, squamous epithelium	0	Yes	Carcinosarcoma
2	Braunwell, B.: Lancet **1**: 170, 1897	1897	25 yr.	F	3 mo.	Aspiration, incision and drainage	Died	Single encapsulated, in right lobe	Spindle cells, adenomatous formations, rudimentary blood vessels	0	Yes	Angiosarcoma
3	Misick, O. S.: J. Path. & Bact. **5**: 128, 1898	1898	6 wk.	M	3 wk.	0	Died	Multinodular, in right lobe	Liver cells in alveolar arrangement, bone plaques, osteoblasts, blood vessels, bile ducts, embryonic liver tissue, epithelial cysts, spindle cells	0	Yes	Teratoma
4	Grünberg: München. med. Wehnschr. **51**: 1037, 1904	1904	2 yr.	..*	.....*	..*	Died	.....*	Spindle cells, cartilage	0	Yes	Sarcoma
5	Marx, H.: Beitr. path. Anat. u. z. alig. Path. **36**: 585, 1904	1904	52 yr.	M	6 wk.	0	Died	Single	Epithelial tissue, blood vessels, syncytial cells	0	Yes	Mixed tumor
6	Philipp, P. W.: Jahrb. f. Kinderh. **68**: 353, 1908	1908	9 mo.	M	.....*	0	Died	Uninodular, in right lobe	Epithelium, bile ducts, chondroblasts, cartilage	0	Yes	Embryonal carcinoma
7	Dominici, H., and Merle, P.: Arch. de méd., expér. et d'anat. path. **21**: 136, 1909	1909	56 yr.	M	.....*	..*	Died	Uninodular, with diffuse seeding of liver	Epithelium, connective tissue, spindle cells	Lung, pancreas, adrenal glands, liver	Yes	Carcinosarcoma
8	Hippel [4]	1910	21 mo.	F	1 mo.	0	Died	Left lobe	Adenomas, embryonal tissue, bile ducts, cartilage, squamous epithelium	0	...*	Embryonal mixed tumor
9	Nakamura, H.: Gann, Ergebn. Krebsf. in Japan **5**, 1911	1911	18 mo.	F	.....*	..*	Died	.....*	Liver cells, bile duct cells, bone tissue	0	Yes	Embryonal tumor
10	Yamagiwa, K.: Virchows Arch. f. path. Anat. **206**: 437, 1911	1911	12 mo.	F	7 mo.	..*	Died	Multinodular	Liver cells, bile ducts, bone elements	0	Yes	Embryonal carcinoma
11	Yamagiwa	1911	18 mo.	F	.....*	..*	Died	Multinodular, in both lobes	Bone tissue, connective tissue, epithelium, cartilage, mucous membrane	0	Yes	Embryonal carcinoma
12	Idzumi, G.: Arch. f. klin. Chir. **100**: 1181, 1913	1913	7 mo.	M	.....*	..*	Died	Uninodular, in right lobe	Glycogen-containing cells, bone tissue, connective tissue, epithelium, cartilage, mucous membrane	0	Yes	Embryonal sarcoma
13	Stranz, H.: Über Mischgeschwülste der Leber, Inaug. Diss., Breslau, B. Elkeles, 1913	1913	12 mo.	F	.....*	..*	Died	Uninodular, of right lobe	Embryonal cells, osteoid cells, connective tissue, epithelium	0	Yes	Mixed tumor
14	Saltykow, S.: Cor.-Bl. f. Schweiz. Ärzte **44**: 385, 1914	1914	57 yr.	M	.....*	..*	Died	Uninodular, of right lobe	Epithelium, bone, cartilage, mucous membrane	0	Yes	Carcino-osteochondromyxosarcoma

Summary of Data on Twenty-Seven Cases of Mixed Tumor of the Liver—Continued

Case No.	Author	Year	Age	Sex	Duration of Symptoms	Treatment	Outcome	Tumor, Gross Characteristics	Histological Elements	Presence of Metastases	Malignancy	Author's Diagnosis
15	Kelemen, A.: Frankfurt. Ztschr. f. Path. **33**: 423, 1926	1920	69 yr.	M	1 yr.	Operated on for gangrene of gall-bladder	Died 3 days after operation	Uninodular, of left lobe	Epithelial tissue in papillary formation, bile ducts, liver cells	0	...*	Papillary cyst-adenoma
16	Sissoew, T.: cited by Nissel [1]	1922	45 yr.	M	.....*	..*	Died	Multinodular, of right lobe	Epithelium, fat, cartilage, nerve, smooth muscle, oral mucosa	Lung	Yes	Mixed tumor
17	Mittasch, G.: Zentralbl. f. allg. Pathol. u. path. Anat. **33**: 67, 1922-23	1922	31 yr.	M	.....*	0	Died	Multinodular, in both lobes	Fat, smooth muscle, blood vessels	0	...*	Mixed embryonal tumor
18	Nissel [1]	1928	Newborn	F	Present at birth	0	Died, lived only a few minutes	Uninodular, of right lobe	Liver cells, bone, cartilage, epithelial cells	0	Yes	Mixed tumor
19	Sheehan [2]	1930	6 yr.	F	6 mo.	0	Died	Uninodular, in right lobe	Myxomatous and fibrous connective tissue, acinar epithelial cells, muscle	Liver	Yes	Embryonal tumor
20	Bittner, W.: Wein. klin. Wchnschr. **1**: 223, 1934	1934	2 mo.	..*	.....*	..*	Died	.....*	Adenomatous epithelial tissue, osteoid tissue, connective tissue	0	...*	Mixed tumor
21	Imai, T.: Tr. Soc. path. jap. **24**: 578, 1934	1934	32 yr.	M	Mass present from infancy	Surgery attempted but tumor was not removed	Died	Uninodular, of right lobe	Epidermis, sweat glands, eye, connective tissue, fat, cartilage, bone, marrow, blood vessels, gonads, bronchial and oral mucosa	0	Yes	Cystic teratoma, with carcinomatous change in squamous cells
22	McRae, F. W.: Am. J. Surg. **28**: 575, 1935	1935	6 mo.	M	2½ mo.	Surgical removal	Died 5 days after operation	Uninodular lobulated, of right lobe	Epithelium in adenomatous formation, keratinized epithelium, osteoid connective tissue, blood vessels	0	Yes	Mixed tumor
23	Condat, J. G., and Lasserre, J.: Arch. de méd. d. enf. **40**: 521, 1937	1937	3 mo.	M	2 wk.	Exploratory laparotomy	Died after operation	Uninodular, of right lobe	Bile canaliculi, liver cells, Kupffer cells, undifferentiated cells	0	...*	Undifferentiated epithelioma
24	Leffers [5]	1941	16 mo.	M	Unknown	0	Died	Multinodular, in both lobes	Adenomas, cartilage, bone, myxomatous connective tissue, liver cells, bile ducts, blood vessels	Lung	Yes	Mixed tumor
25	Yarbrough, S. M.: Texas State J. Med. **40**: 426, 1944	1944	6 wk.	F	? from birth	Surgical removal	Recovered; well 3 yr. later	Uninodular, in right lobe	Epidermis, connective tissue, fat, intestinal bronchial mucosa, squamous epithelium, blood vessels, pancreas, liver, brain	0	...*	Teratoma
26	Hartz and van der Sar [3]	1945	4 mo.	F	Present at birth	0	Died	Uninodular, in right lobe	Squamous epithelium, hair, sebaceous glands, gastric mucosa, nerve, striated muscle, cartilage	Similar tumor of umbilical cord at birth	No	Benign teratoma
27	Grayzel and Milman	1947	6 yr.	M	4½ yr.	Surgical removal	Died 31 mo. after operation	Uninodular, of right lobe	Liver cells, rudimentary bile canaliculi, myxomatous connective tissue, epithelial cells in alveolar arrangement	Lung, brain	Yes	Mixed tumor

* No record.

entiation or from two or more primary germ layers. Krafka's [6] explanation of the origin of teratomas was based on the so-called organizer theory of embryology. The organizer, located in the posterior part of the neural fold, is a zone in the primitive embryo which "induces neighboring tissues to follow the axial plan of organization." A secondary organizer developing early might stimulate the formation of a secondary embryonic axis and lead to the development of a teratoma. Krafka cited in support of his theory the fact that most teratomas in man are located in close proximity to the organizer zone (Hensen's node). Thus, most teratomas are found in the sacrococcygeal, urogenital and branchiogenic regions. He named three regions which he claimed were free of teratomas, owing to mechanical interference with the development of a secondary organizer zone. These were the heart, the limbs and the liver. Yet Christy [7] reported a case of malignant teratoma of the arm, and Beck [8] reported a case of intrapericardial teratoma. These exceptions serve to indicate that in the case of teratomas, as with all tumor growths, the precise etiology is still to be elucidated.

Seventeen tumors (63 per cent) were single, 7 tumors (26 per cent) were multinodular, and of 3 tumors the gross characteristics were not specified. In 15 cases (56 per cent) the tumor was found in the right lobe alone; in 2 cases (7 per cent), in the left lobe, and in 3 cases, in both lobes; in 7 cases the location was not specified. Thus, the growth appeared to be chiefly uninodular and involving the right lobe of the liver. In 20 cases (74 per cent) the tumor was considered to be malignant and in 1 case benign, and in 4 cases no mention of malignancy was made; in only 5 cases (19 per cent) were metastases reported, and in 1 case there was in addition a similar tumor of the umbilical cord.

No treatment was undertaken in 9 cases and presumably not undertaken in 11 more in which no reference to therapy was made; some form of surgery was undertaken in 7 cases, and the tumor was removed in 3 cases, only once with complete recovery.

The case herein reported had several interesting features. The tumor was known to have been present for 4½ years before operation and was obviously malignant on microscopic examination. Yet there were no evidences of metastases or of recurrence at the primary site until one year after operation. The presence of the mass exerted several physiological effects which were reversed after removal, namely, the electrocardiographic changes, the low glucose tolerance curve and the hypertension. Histologically, the tumor was bizarre and presented considerable difficulty of classification. It assumed no distinctive cytoarchitectural pattern, despite the fact that it was made up of three distinct cell types. The solid cords and masses of large cells bore at least a superficial resemblance to liver cells, although they might have been interpreted as adrenal cortical cells. There were also tubular structures suggestive of primitive biliary ducts. The third cell type could not be identified with any mature liver cell element. The connective tissue was of a primitive myxomatous character. The bizarre

6. Krafka, J.: Teratoma: An Explanation of its Cause Based on the Organizer Theory of Embryology, Arch. Path. **21**:756 (June) 1936.

7. Christy, C. J.: Malignant Teratoma of the Arm, Ann. Surg. **116**:948, 1942.

8. Beck, C. S.: Intrapericardial Teratoma and Tumor of the Heart, Ann. Surg. **116**:161, 1942.

nature of the tumor was clearly demonstrated by the varied interpretations offered by the several consulting pathologists of the Tumor Registry of the American Academy of Pediatrics.[9] The diagnoses varied from mixed embryonal tumor to pheochromoblastoma and adrenal tumor.

SUMMARY AND CONCLUSIONS

A case is reported of mixed embryonal tumor of the liver in a boy of 6 years. The tumor was removed, but the child died of metastases 31 months after operation.

A review of the literature disclosed 26 similar cases, 67 per cent of which occurred in children. Malignant characteristics were found in 74 per cent of cases, while metastases were observed in only 19 per cent. Surgical treatment was successful in only one case of the seven in which it was undertaken. The low incidence of metastases and the tendency toward uninodular growth suggest that early surgery may offer hope of cure in this disease.

9. Personal communication to the authors.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

TRANSMISSION OF IMMUNE ANTIBODIES FROM MOTHER TO CHILD. J. SCHUBERT and A. GRÜNBERG, Schweiz. med. Wchnschr. **79**:1007 (Oct. 22) 1949.

Intracutaneous vaccination was done on 40 women during the second half of pregnancy. A vaccine made from typhoid bacilli was used. Agglutination titers were determined with the flagellate H agglutinin used as antibody. Shortly after birth the titer of colostrum was usually much higher than that of the mother's blood. The agglutinin appears in colostrum at the same time as in blood. A decline in the titer occurs sometimes during the first day and usually on the second, and the decline proceeds in direct proportion to the amount of milk. Usually after the third week the agglutinin can no longer be found. On passive immunization the agglutinin could also be demonstrated in colostrum. The cord blood from the newborn infant contained agglutinin in five cases (about 15 per cent); the titer was equal to that of the mother's blood in two cases, and in the three others it was much lower. Agglutinin persists in the infant's blood for weeks. Vaccination of the newborn infant did not lead to agglutinin production. On passive immunization of the newborn the agglutinin disappeared more rapidly than in the cases mentioned above. The milk secreted by the newborn did not contain agglutinin. In cases in which the cord blood proved to be free from agglutinin, it could not be found when their infants were fed milk rich in this antibody. In cases in which the cord blood contained agglutinin, its titer could not be raised in the blood by the feeding of such milk. Agglutinins could be demonstrated in such cases in the stool, although peptic digestion in titer rapidly destroys it.

AMBERG, Rochester, Minn.

Metabolism; Infant Feeding; Milk and Other Foods

THE IMPORTANCE OF THE AMINO ACID CONTENT OF THE BLOOD IN REGULATING GROWTH PROCESSES. P. PINNA, Lattante **19**:513 (Sept.) 1948.

Determinations were made of the amino acid content of the blood of 22 children on various diets and of ages ranging from 1 month to 15 years. The blood amino acid content varied between 6.0 and 16.0 mg. per 100 cc., the mean content being 10.96 mg., a figure definitely higher than those given in other reports from the literature. The amino acid content in the urine varied directly with that of the blood. There was a diminution in the blood amino acid content after the injection of epinephrine. The belief is expressed that the amino acid content of the blood is not exclusively controlled by the function of the liver.

HIGGINS, Boston.

A COLORIMETRIC METHOD FOR THE DETERMINATION OF SODIUM IN BIOLOGIC FLUIDS. P. MENGHI, Minerva Pediat. **1**:303 (Aug.) 1949.

The method is based on the intensity of the yellow color of a watery solution of the precipitate formed by the action of zinc uranylacetate with sodium. Directions for determination of sodium in blood serum are given.

HIGGINS, Boston.

THE USE OF BETA LACTOSE IN INFANT FEEDING. FRITZ PETUELY, Policlinico inf. **15**:382 (Aug.) 1947.

The negative result in control studies by Dawini on the use of beta lactose in infant feeding must have been due to the substance used, which was not a pure product but a racemic one.

FROM THE AUTHOR'S SUMMARY.

EXCRETION OF CREATININE IN BABIES. OSCAR CORREA B. and HUMBERTO DEL POZO P., Rev. chilena de pediat. **19**:243 (March) 1948.

Results are reported of determinations of the excretion of creatinine done on 94 infants, 23 days to 2 years of age, with various nutritional conditions. In a previous work of one of the

authors, the lack of value of the creatinine coefficient as an index of nutritional state in infancy was demonstrated, and in its place a new coefficient, creatinine-height coefficient (milligrams of creatinine per 24 hours divided by centimeters of body height), was suggested. Accordingly, a comparative study of the two coefficients was undertaken. The following conclusions were drawn:

1. Owing to physiological causes inherent in age, especially a high relative proportion of fatty tissue and water, Shaffer's coefficient does not give as accurate a view of the nutritional condition of infants as it does of children of school age and of adults.

2. Unlike this index, the new creatinine-height coefficient appears to be a reliable method of appraisal in such a field.

3. The statistical analysis of the data reveals that differences among values of the new coefficient are statistically significant, a result that is not found among those of Shaffer's coefficient.

FROM THE AUTHORS' SUMMARY.

DISTURBANCES IN THE METABOLISM OF CAROTENES IN THE CHILD. A. CASTELLANOS, Rev. cubana pediat. **20**:377 (July) 1948.

The author gives a review of the knowledge of the variations in metabolism of carotenes, dividing carotene disturbances (or dyscarotinosis) into: (1) hypercarotinosis (carotinosis cutis with hypercarotinemia; carotinosis cutis without hypercarotinemia, or hypercarotinemia without carotinosis cutis) and (2) acarotinosis (normal skin color with acarotinemia).

He states that excess carotene in the diet is not the only factor in the occurrence of carotinosis cutis and that two other factors are thyroid insufficiency and hepatic insufficiency. The correction of hypothyroidism and improvement in hepatic function may be sufficient, without change in diet, to restore the skin to its normal color.

Acarotinoses are conditions in which carotinoids are absent from the blood. This occurs frequently in severely toxic or dystrophic infants and is associated with hypovitaminosis due to lack of vitamin A.

KEITH, Rochester, Minn.

METHODS OF PROVING DAMAGE FROM HUNGER IN CHILDHOOD. H. EWERBECK, Monatsschr. f. Kinderh. **97**:116, 1949.

Using the congo red method of determining blood volume, the author found an average decrease of 17 per cent in eight of 14 undernourished children ranging in age from 9 to 14 years. Their red blood cell counts and hemoglobin values were within normal limits. However, when an adjustment was made for the decreased circulating blood volume, a marked anemia was evident.

Creatinine excretion in the urine was high in some patients but low in others obviously undernourished and underweight. Serum albumin values remained almost normal, while there was a marked drop in the globulin fraction. In adults with malnutrition low albumin values are common, which may explain why "hunger edema" is frequently seen in adults and not in children.

HARTENSTEIN, Chicago.

TREATMENT OF MALNOURISHED INFANTS WITH METHYLTHIOURACYL. M. SZABÓ, Orvosok lapja, **4**:566 (April 25) 1948.

Szabó treated five malnourished infants "for diminishing the increased oxidation" with methlythiouracil and found a quick gain in body weight.

O. GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

ROENTGEN RAY TREATMENT OF MASTITIS DURING CHILDBED AND BREAST FEEDING. F. SZELLŐ, Orvosok lapja **4**:992 (Aug. 1) 1948.

Acute puerperal mastitis can be cured with roentgen ray treatment in 96.5 to 100 per cent of cases if irradiation is performed within 24 to 48 hours respectively. Frequently the annoying symptoms cease in a few hours, often suddenly. Regression of the infiltration follows soon after. Roentgen radiation has proved itself beneficial also for those patients suffering from

a seropurulent process. In long-lasting cases an especially favorable response is shown if irradiation coincides with the first phase of an acute exacerbation.

O. Görgényi-Göttche, Budapest, Hungary.

A Method of Artificial Feeding. Josef Svejcar, Pediat. listy, 1949, no. 1, p. 1.

The author describes an original method of artificial feeding of infants and small children in the first and second year of life which he believes to be the best suited for Czechoslovakia.

From the Author's Summary.

Extension of the Sanborn Tables for the Calculation of the Basal Metabolism in Children from Six to Fourteen Years. Severin Daum, Pediat. listy, 1949, no. 1, p. 155.

The author reports on the tables for children under 14 years which were used in the examination of the basal metabolic rate of 3,200 children. From the Author's Summary.

Treatment of Acute Disturbances of Nutrition by Potassium Solution. Kornel Chmelo, Ludovit Orich and Elena Furdíková, Pediat. listy, 1949, no. 3, p. 101.

Good results were obtained in the treatment of acute disturbances of nutrition by the introduction of potassium solution. In rehydration a 10 per cent solution of glucose was used with 1.15 per cent calcium chloride, 1.3 per cent sodium hydrogen carbonate and 0.9 per cent sodium chloride. A detailed description of the authors' own procedure is given.

From the Authors' Summary.

A Preliminary Report on the Effect of Procain Hydrochloride in Toxicosis. Vilém Jirí Mathesius, Pediat. listy, 1949, no. 3, p. 106.

The author gives a report based on his own observations of the favorable effects of procaine hydrochloride in 52 cases of toxic enteritis. From the Author's Summary.

A System of Artificial Feeding. Otakar Teyschl, Pediat. listy, 1949, no. 3, p. 115.

The author gives a review on the feeding of infants in the first year of life as practiced at the children's clinic in Brünn. From the Author's Summary.

Vitamins; Avitaminoses

The Availability of Vitamins from Yeasts: V. Differences in the Influence of Live Yeast on the Absorption of Pure Thiamine Hydrochloride, Pure Riboflavin and Nitrogen by Human Subjects and the Effect of Distribution of the Vitamin Doses. Marcella Garber, Mona M. Marquette and Helen T. Parsons, J. Nutrition **38**:225 (June) 1949.

A higher percentage of a dose of thiamine hydrochloride was returned in the urine of human subjects when the supplement was ingested with meals rather than between meals. The urinary return of riboflavin was not similarly influenced. Garber and co-workers found that pure thiamine hydrochloride ingested with fresh bakers' yeast failed to be returned in the urine, presumably through almost complete failure of absorption by the digestive tract. The same effect was observed when food thiamine was ingested with live yeast. The "interference" by fresh yeast is not, then, attributable per se to the effect of an antienzyme in the digestive tract.

In the same experiment live yeast interfered less with riboflavin than with thiamine in that only the riboflavin of the live yeast cell, not that in the food or in pure form, appeared to be withheld from absorption; nitrogen was least affected, inasmuch as an average of 80 per cent of the nitrogen of the yeast cell itself was returned in the urine. The hypothesis presented was that food thiamine is interfered with by live yeast because of competition between the absorbing membranes of the live yeast cell and those of the digestive tract, with a resulting retention of the absorbed thiamine within the yeast cell. Fredeen, Kansas City, Mo.

A Paradoxical Relationship Between Serum Level and Liver Content of Vitamin A. R. F. Krause, J. Nutrition **38**:535 (Aug. 10) 1949.

R. F. Krause concluded from the evidence gained from this study plus the observations described by other workers that it is difficult to assess the body's need or its reserve of vitamin A on the basis of blood level per se. The evidence presented supports the hypothesis that there is a regulatory mechanism controlling the blood vitamin A level of rats which operates to give an inverse relation between the blood level and liver content of vitamin A. This regulatory process was found to function in both normal male and female rats and also in those females subjected to vitamin A depletion. In general, the male rats were more severely depleted of their vitamin A liver stores in a period of four weeks than were the females over a 20 week period. It is suggested on the basis of the inverse ration that perhaps tissue demand is a more potent factor governing serum blood levels than is liver depot content. Various factors such as age, sex, disease and amount of vitamin A stored undoubtedly affect this relation. It is difficult to assess the body's need or its reserve of vitamin A on the basis of blood level per se.

Fredeen, Kansas City, Mo.

Further Observations on the Absorption of Vitamin A: Influence of the Particle Size of the Vehicle on the Absorption of Vitamin A. J. M. Lewis, Sidney Q. Cohlan and Angelina Messina, Pediatrics **5**:425 (March) 1950.

Experiments carried out with infants revealed that vitamin A as it occurs naturally in milk was more effectively absorbed than when administered in an oily vehicle but not as well absorbed as when given in an "aqueous" preparation. The high degree of absorbability of vitamin A in milk is due to the relatively small particle size of the butter fat globule.

By reducing the particle size of a fish liver oil preparation (percomorph liver oil) to 1 to 2 microns, by homogenization into milk or water, the absorption of vitamin A was considerably enhanced in children and in rats.

The relation of the particle size of the vehicle used for vitamin A to absorption was further demonstrated by the results of administration of three vitamin A preparations of varying particle size to children and rats. The highest absorption occurred after the administration of a preparation ("aqueous") containing particles of submicroscopic proportion; the lowest absorption resulted after the administration of a preparation (oil) containing particles macroscopic in size, and intermediate absorption was observed after the use of a preparation (emulsion) containing particles varying in size from 1 to 20 microns.

Similarly, in a child having cystic fibrosis of the pancreas, the absorption of vitamin A was dependent on the particle size of the vehicle employed. From the Authors' Summary.

Effects of a Single Massive Dose of Vitamin D in Rickets. G. Mouriquand and D. Dechavanne, Presse méd. **56**:672 (Sept. 29) 1948.

The authors present the roentgenograms of two infants who showed the changes of advanced rickets. After the administration of a single dose of 15 mg. of vitamin D_2 marked improvement occurred. The authors warn against repeated massive doses.

Daffinee, Melrose, Mass.

The Limits of the Influence of Vitamin C on Capillary Resistance. G. M. Dore and P. Pinna, Ann. ital. di pediat. **1**:80 (Dec.) 1948.

The authors have studied the limits of action of vitamin C on capillary fragility, on amount of ascorbic acid in the blood and in the urinary elimination, which they estimated before and after administering vitamin C and vitamin K to healthy children.

Although noticing in some cases an improvement in capillary resistance after administration of vitamin C, they could not fix a sure relation between capillary alteration and scarcity of vitamin C.

They suppose, then, that other factors may work on the former with the same mechanism or a mechanism different from vitamin C.

From the Authors' Summary.

ASCORBIC ACID IN THE DISEASES OF NUTRITION DURING THE FIRST BIENNIUM. T. CAPECCHI, Arch. ital. pediat. e puericolt. **12**:309, 1948.

The author's researches were concerned with the behavior of blood and urine ascorbic acid and with vasal fragility in children under 2 years of age affected by the following diseases: dystrophy and atrophy, dystrophy from carbohydrates, toxic dyspepsia either primary or secondary to parenteric troubles, food poisoning and enterocolitis with or without toxic condition.

In the nonparenteric cases the blood ascorbic acid values were in 1 case 0.91 mg. per 100 cc.; in 13, from 0.90 to 0.60; in 16, from 0.60 to 0.40, and in 12, below 0.40. The lowest pathological values were seen in food poisoning. In the parenteric cases the blood ascorbic acid values were about 1 mg. in two cases and from 0.57 to 0.70 mg. in two cases.

As a rule, the blood ascorbic acid values would diminish when the condition grew worse and increase when it improved.

Urinary elimination ranged between 0.20 and 0.40 mg. per kilogram daily for hematic values below 0.60 mg. per 100 cc. It reached 0.70 to 1 for rheumatic values above 0.6 mg.

The vasal fragility was increased in 42 per cent of the cases and was accompanied with low blood ascorbic acid values.

The administration of vitamin C by oral or parenteral route was followed by a sudden increase of urine ascorbic acid, normalization of the blood ascorbic acid within a few days and, as a rule, a subsequent normalization of the vasal fragility.

FROM THE AUTHOR'S SUMMARY.

REACTION OF ASCORBINEMIA, VESSEL RESISTANCE AND TESTS FOR SATURATION OF VITAMIN C IN THE INFANT. G. MAGGIONI and A. BORSATTI, Arch. ital. pediat. e puericolt. **13**:3, 1949.

The authors have examined 26 children; of these, 10 were affected with scurvy of different degrees of severity, 7 with typhoid or paratyphoid, 4 with postdiphtheric paralysis and 5 with other diseases. In all children ascorbinemia, vasal fragility and ascorbinuria were tested before and after the administration of large doses of vitamin C (intramuscular injections of 200 mg. of ascorbic acid daily). The period required to reach saturation varied without any relation to the initial ascorbinemic concentrations, while the abrupt increase of ascorbinuria was a constantly observed feature.

In patients with scurvy the vasal resistance began to increase at the saturation point but became normal only after a week, while in typhoid patients normal findings were obtained immediately at the moment of saturation. The behavior varied in the other patients.

Saturation values for ascorbinemia have always been over 1.60 mg. per 100 cc.

According to the authors, the three tests (vasal fragility, ascorbinemia and saturation), if executed at the same time, are quite sufficient for recognition of the different degrees of hypovitaminosis C.

FROM THE AUTHORS' SUMMARY.

THE EFFECT OF INHALATION OF IRRADIATED AIR ON THE BLOOD CALCIUM AND PHOSPHORUS OF RACHITIC AND SPASMOPHILIC CHILDREN. L. SPOLVERINI, Clin. Pediat. **29**:1 (Jan.) 1947.

The blood calcium and phosphorus levels showed elevations corresponding with clinical improvement in 14 infants with spasmophilia and/or rickets after the inhalation of irradiated air. The treatments were given daily for 10 to 21 days; the child would be in a room for 20 minutes breathing air which had been irradiated by a quartz mercury vapor lamp but would not be exposed directly to the ultraviolet rays.

HIGGINS, Boston.

VITAMIN A AND CAROTENE IN MILK. D. SPISNI, Lattante **18**:399 (July) 1947.

This article reviews the literature and summarizes the present knowledge regarding the vitamin A and carotene content of milk.

HIGGINS, Boston.

THE RENAL FUNCTION IN RICKETS. A. GIUA, Lattante **18**:463 (Aug.) 1947.

Renal function was studied in 13 children under 5 years of age; in each child the function was normal. However, of two rachitic dwarfs, 5 and 6 years of age, one did show inability for

normal concentration of the urine; the other child's urine contained albumin and red and white blood cells, which disappeared after two weeks' treatment of the child with vitamin D.

HIGGINS, Boston.

THE ACTION OF VITAMIN A ON THE GROWTH OF BONE IN INFANTS. P. BRUSA, Lattante **19**:653 (Nov.) 1948.

Observations were made on 19 children about 4 months of age. Twelve of the infants received injections of 25,000 units of a vitamin A preparation containing no carotene or vitamin D every five days for four months. Seven infants served as controls. The diets of the two groups were comparable, consisting of breast or artificial feedings.

The infants receiving the vitamin A showed greater gains in weight, height and bone growth. However, the infants receiving vitamin A showed some signs of rickets on roentgenograms which were not found in the control infants. The conclusion drawn from this study is that an antagonism exists between vitamins A and D.

HIGGINS, Boston.

EXPERIMENTAL RESEARCH ON THE ACTION OF VITAMIN D_2 ADMINISTERED IN LARGE DOSES. GINO BROGI, Riv. di clin. pediat. **44**:583 (Sept.) 1948.

The author has investigated the action of shock doses of vitamin D_2, injected parenterally, on rats nourished normally and on rats on a rachitogenic diet, confirming its low toxic action even when employed in enormous doses, at least in experimental animals.

The animals showed an almost normal growth, and in some organs (kidney, aorta) no accumulation of calcium salts was noted.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF RICKETS IN PREMATURE INFANTS WITH VITAMIN D_2 SHOCK. JOSE ALBERTO SALGADO LANZA and MARIANO C. SAIZAR, Arch. de Pediat. d. Uruguay **20**:369 (June) 1949.

A report is made of the results of a study of 27 premature infants, some with evident signs of rickets, others with slight manifestations of this disease. In only 17 could a complete three-fold study—clinical, roentgenographic and blood examination—be made; in the other 10 the study was incomplete. The following was the work schedule: (1) prove the existence of clinical signs of rickets; (2) investigate the values of calcium, phosphorus and phosphatase, and (3) perform roentgen study of the long bones. The vitamin shock was effected in most cases by mouth, 15 mg. (600,000 units) of vitamin D_2 being given. In a smaller proportion of cases the intramuscular route was used, the doses varying between 200,000 and 600,000 units. All subjects were premature infants weighing between 920 and 2,500 Gm. Among the clinical signs was the incidence of soft spots in the skull. The blood calcium level rose to an average of 8.5 mg., the minimum and maximum values being 7.6 and 10.20 mg. per 100 cc. respectively. The inorganic phosphorus gave an average of 4 mg. per 100 cc., with extremes of 3.84 to 5.8 mg. The phosphatase gave values between 9.12 and 30.1 units, with an average of 20 units. Roentgenographically five patients presented clear signs of rickets; in the others these were not so evident. A month after the shock, all the examinations and analyses were repeated. In most patients the soft spots in the skull appeared totally or partially cured; the general condition improved, and the calcium and phosphorus levels returned to normal in 1 to 3 months, as did the roentgenographic symptoms. In several cases the roentgenographic control was repeated four or five months later.

FROM THE AUTHORS' SUMMARY.

OBSERVATIONS ON THE VARIATIONS OF VITAMIN C CONTENT IN MOTHERS' MILK. MÜNIRE YÜCEOGLU, Ann. paediat. **173**:142 (Sept.) 1949.

Investigations of the vitamin C content of breast milk carried out during the four seasons showed great differences in the average values. These were in spring, 3 mg. per 100 cc; in summer and autumn, 8 mg., and in winter, 2.4 mg. The reason for these differences seems to lie in the way of living of the population, since the diet contains more or less fruits and vegetables according to the season.

The economic situation influences nutrition and so is responsible for considerable difference of vitamin C content of the breast milk of women of different social layers. The vitamin C content of the milk of women who were well off was 9.5 mg. per 100 cc.; of those in the artisan class, 5.9 mg. and of those in the poorer class, 2.9 mg. These differences are shown to be even greater if one takes the variations in the different seasons into consideration.

On the base of observations made on a group of dystrophic breast-fed infants and in comparison with the occurrence of rickets in breast-fed children, the question is discussed whether and to what degree occult hypovitaminoses play a part in the development of dystrophy in sucklings.

FROM THE AUTHOR'S SUMMARY.

HYPOVITAMINOSIS AND HYPERVITAMINOSIS. A. VAN WESTRIENEN, Maandschr. v. kindergeneesk. **17**:1, 1949.

Principally owing to oversterilization of milk after the war, incidences of scurvy (Barlow's disease) are not exceptional. The clinical signs are discussed. The active fixation of the painful joints helps to distinguish the illness from poliomyelitis and rachitis. Some cases with unusual findings are reported. Roentgenograms in one case show the calcification of a large subperiosteal hematoma, with reconstruction of the femur after treatment with ascorbic acid. One year later the femur was still very broad and massive but much better accommodated to its function. Report is made of an infant who was suffering from hyperhidrosis also and who had lost a considerable amount of vitamin C with its sweat. After oral administration of vitamin B_1 the hyperhidrosis was stopped in three days.

Overdosage of vitamin D is not exceptional nowadays, and signs of mild intoxication are not infrequent. After a partial review of the literature van Westrienen discusses the features of a clinical picture that is rapidly becoming well known, namely, severe loss of appetite with polydipsia and polyuria, resulting in retardation of growth and loss of weight. Fever, increased sedimentation rate and leukocytosis that cannot be explained by other causes are also seen. Laboratory examinations frequently show anemia with leukocytosis, hypercalcinemia and, finally, uremia when the function of the kidneys is badly damaged by calcinosis. Decalcification of the skeleton may follow and if misunderstood may result in treatment with ultraviolet rays and increased supply of vitamin D. After a discussion of massive dose therapy van Westrienen recommends selective care and states a preference for regular treatment with small doses. The observations of Hottinger, who demonstrated retention of calcium in rachitic children after vitamin D was given but hypercalciuria with an important lowering of the balance of calcium in nonrachitic children, are mentioned. Three cases of moderate overdosage with typical findings are reported.

VAN CREVELD, Amsterdam, Netherlands.

THE SIZE OF THE ERYTHROCYTES IN AVITAMINOSES OF THE RAT. R. JÜRGENS and A. STUDER, Schweiz. med. Wchnschr. **78**:1066 (Oct. 30) 1948.

Deficiency of vitamins B, D and K leads to microcytosis in the rat; deficiency of vitamins A, E and biotin, to macrocytosis. With deficiency of vitamins B_3, B_6 and pantothenic acid the diameter of the red blood corpuscles remain normal.

AMBERG, Rochester, Minn.

ROLE OF VITAMIN INSUFFICIENCY IN THE PATHOLOGY OF THE CORNEA. A. KATZNELSON, Vestnik oftal. **26**:3, 1947.

Keratomalacia due to avitaminosis A in the mother is observed in infants, who may be born with dense opacities of the cornea. According to Katznelson's observations, the clinical picture varies in adults and in infants: Avitaminosis A is an early manifestation in infants, while in adults it appears later, possibly because of a reserve of provitamin A in the tissues. The characteristic involvement of the skin and mucous membranes in adults with keratomalacia is less evident in children. Both eyes are usually affected in children, while frequently in adults there is an interval between the involvement of the first and that of the second eye. The secondary purulent infection associated with keratomalacia is less severe in children. The course of the disease in patients with trachomatous pannus is atypical and frequently leads to diagnostic

mistakes. In general, the process is more favorable in cases of vascularized corneas. Dystrophy of the cornea occurring in the course of diabetes and toxic diffuse goiter can be explained by endogenous avitaminosis A. The author observed true keratomalacia in a patient with acute hyperthyrotoxicosis. Lagophthalmic keratitis complicating infectious diseases may also be due to endogenous avitaminosis A. Tuberculous-allergic diseases of the eye are commoner in children with poor nutrition. The cutaneous reaction to tuberculin is also lowered in these children.

The author observed cases of disciform, herpetic keratitis due to thiamine insufficiency. There is a similarity in the clinical picture of neurotrophic and that of neurogenic keratitis of virus origin. The treatment of herpetic keratitis with intravenous injections of thiamine and local application of thiamine ointment gave good results.

Ariboflavinosis causes disturbance of the epithelium of the cornea and increase of the marginal loop vessels, rosacea keratitis and marginal ulcers. Administration of riboflavin is therefore indicated in treatment of these diseases of the cornea. Ascorbic acid is indicated in cases of phlyctenas and tuberculous keratitis and in chemical and thermal burns of the cornea. In the latter, 40 per cent dextrose solution with large doses of ascorbic acid led to a decided lessening of pain, and inflammatory reaction and to decrease in the secondary trophic disturbance of the cornea, with formation of thin scars.

SITCHEVSKA [ARCH. OPHTH.].

ANGULAR BLEPHARITIS IN ARIBOFLAVINOSIS. CHEN TZU-TA, Chinese M. J. **66**:1 (Jan.) 1948.

Angular blepharitis in riboflavin deficiency was first reported by Golpalan in India in 1946. In addition to the classical signs of the deficiency, certain patients displayed moist, shallow, slightly inflamed erosions at the outer angles of the eyelids. Chen Tzu-Ta has observed a total of seven additional similar cases in China.

MACDONALD, Pittsburgh.

Hygiene; Growth and Nutrition; Public Health

STATISTICAL CONSIDERATIONS ON THE MORTALITY IN A PEDIATRIC WARD OF A HOSPITAL FROM 1931 TO 1946. M. BERNHEIM, M. JEUNE and EYSSERIC, Pédiatrie **36**:293 (July-Aug.) 1947.

A statistical evaluation was made by one of the authors of the mortality rate during the last 15 years in the Colrat pediatric ward of the Debrousse Hospital in Lyons, France; data from infants up to 2 years of age, with the exception of debilitated infants or premature infants of a few weeks of age, were used. The study showed a progressive reduction in mortality rate from 40.25 to 30.08 to 24.26 per cent in the three five year periods. The last figure is particularly remarkable, because the general infant mortality rate in France had increased from 7 to 10 per cent. The most important causes of death were tuberculosis, acute pulmonary infections, diarrhea, toxicosis and athrepsia; about half the deaths were from the last three mentioned.

In many of the cases there was otomastoid and meningoencephalitic origin or complications. The most frequent direct or underlying cause of admission in 1946 was "common infection of the nursling" (infection of the upper respiratory tract?). The recognition of this fact has caused the authors to alter the therapeutic approach, which has led to the improvement of the mortality rate. The authors state that the number of these infections has increased rapidly during the last years but that virologic studies have not been made to determine their origin.

GLASER, Chicago

PRESENT PROBLEMS IN SOCIAL WORK AMONG INFANTS AND THE ACTIVITY OF THE O.N.M.I. IN THE POSTWAR PERIOD. L. D. VERONESE, Lattante **20**:321 (June) 1949.

The social problems concerning the Italian children center about (1) the illegitimate child, (2) the abandoned child, (3) the child exposed to tuberculosis, (4) breast milk centers, (5) illiteracy, (6) education of the mothers, (7) day nurseries in cases in which the mother works and (8) nursing personnel and schools for nurse's aides.

The O.N.M.I. (Opera Nazionale per la Protezione della Maternita e dell' Infanzia) has assumed the functions previously taken care of by UNRRA. There have been 226,015 mothers visited, 71,658 being cared for in maternity homes and 56,936 children have been placed in homes or institutions.

HIGGINS, Boston.

THE DERIVATIVE CURVES IN THE STUDY OF GROWTH IN CHILDREN. I. GOBESSI, Policlinico inf. **16**:427 (Sept.) 1948.

Gobessi applies the methods of calculus to the growth curves of children. Thus, growth in height is a function of time (speed!), while variation in the rate of growth is a second derivative thereof (acceleration!). Similarly, gain in weight is a function of time, and rate of change in rate of gain in weight is the second derivative.

HIGGINS, Boston.

SOCIAL ASSISTANCE TO THE CHILD IN DURAZNO. GRACIA SCAFFO DE CASAS MELLO, Arch. de pediat. d. Uruguay **20**:225 (April) 1949.

After taking possession of the post of chief of the children's service in the Durazno Hospital, located in the interior of Uruguay, the author felt it necessary to seek a remedy for the causes of infant mortality in that place. She began by organizing a commission for the protection of infants, gave classes to social workers and founded a nutrition clinic for preschool children, a home, a dining room for mothers and children and a child welfare clinic (*Gota de Leche*). The result obtained can be appreciated when it is known that the entrance of sick children to the hospital has been reduced 30 per cent. The author organized in the same dining room an office which attends to matters with reference to the child and his family. She has also opened an emergency home for girls in social trouble. The benefit of this work is pointed out, and the help obtained from the Consejo del Niño del Uruguay, the Ministerio de Salud Pública, the society of Durazno and others is mentioned.

FROM THE AUTHOR'S SUMMARY.

THE NEGLECTED CHILD: HIS SOCIAL REHABILITATION BY MEANS OF ADOPTION AND ADOPTIVE LEGITIMATION. ROBERTO BERRO, Bol. Inst. internac. am. de protec. a la infancia **22**:48 (March) 1949.

In spite of the advance of means destined for prevention of abandonment, there always is an important number of physically or morally abandoned children. The most advisable measure to assure the education and happy reinstatement of the child in the social environment is to give him a foster home. The work sets aside the problem of family placement studied by Dr. Berro in other works published in the bulletin in order to praise and mention the good results obtained by adoption and adoptive legitimation, according to Uruguayan laws. The first one is contained in the Children's Code of 1934 and the second has been published in November 1945.

FROM THE AUTHOR'S SUMMARY.

THE DECLARATION OF CARACAS ON CHILD HEALTH: ITS ORIGIN, SCOPE AND FUTURE RESULTS. VÍCTOR ESCARDÓ Y ANAYA, Bol. Inst. internac. am. de protec. a la infancia **23**:140 (June) 1949.

The author reveals the origin of the Declaration of Caracas and the trend of events which occurred until the definite text was reached. Afterward he deals with the leading principles of this document that have an explicit relation to the health of the children of the Western Hemisphere. He makes evident its special nature which will make it not a dead letter but a series of declarations that will incite improvement in the welfare of children with the aid of the health department.

The declaration establishes first of all the right that the child has to health. It refers also to preventive medical measures, to the treatment of disease and to the aid which must be given to the home and to the child and attaches considerable importance to educational problems. It suggests to the faculties of medicine the need of a greater development in the teaching of pediatrics and puericulture.

It has special recommendations for each age of the child, and after insisting on nutrition and mental hygiene, it concludes by affirming that all children of the Western Hemisphere, regardless of race, color or creed, have a right to take advantage of all opportunities that allow them to develop a healthy, happy and peaceful life.

FROM THE AUTHOR'S SUMMARY.

THE LAW OF JUVENILE COURTS. JOSE L. ARAYA, Bol. Inst. internac. am. de protec. a la infancia **23**:156 (June) 1949.

Dr. Araya comments on the new law (3461) on juvenile courts recently approved in the province of Santa Fe (Argentina) that supersedes, after many years of experience, the law dictated in 1939.

Among other things, the author emphasizes the replacement of the legal prosecutor by the children's agent; the extension of medical services in the home of the minor; the establishment of a social service department; the humanization of the proceedings for establishment of paternity for feeding purposes; the authorization given to the judge of the juvenile court for taking in exceptional cases some general dispositions when confronted by minors who cannot be classified as abandoned or neglected, and the functional identity of the juvenile court as contrasted with courts of common justice.

The new provisions tend to be educatory rather than punitive and are based on experience acquired not only in Argentina but in the other countries of Latin America.

FROM THE AUTHOR'S SUMMARY.

STUDY OF A DRAFT OF AN AMENDMENT TO THE CHILDREN'S CODE OF URUGUAY. JULIO A. BAUZA, ROBERTO BERRO and VICTOR ESCARDÓ Y ANAYA, Bol. Inst. internac. am. protec. a la infancia **23**:194 (June) 1949.

The authors, with long experience in the problems of the protection of children, present and comment on a proposal for the revision of the first part of the present Children's Code of Uruguay.

They begin by presenting the reasons that have led to the proposed changes, which come as a result of 15 years' activity of the Children's Council and its dependencies. At the end they present the text of the proposed new articles of this code.

FROM THE AUTHORS' SUMMARY.

PLACING NEGLECTED CHILDREN IN FOSTER HOMES, TEMPORARILY OR DEFINITELY. JOSÉ PEDRO ACHARD, Bol. Inst. internac. am. de protec. a la infancia **23**:215 (June) 1949.

The author refers to the need of caring for both the body and the spirit of the child, recalls that the home is the place where the child acquires a perfect and harmonious individuality and states that for this reason, children lacking their own home or having an inadequate one must be given a foster home.

He analyzes a variety of cases of children needing foster home care and points out the necessity for a careful investigation of the conditions of the new homes, as well as of the children's characteristics, emphasizing that this will be the task of the social worker.

He also analyzes the placement of children in foster homes either on a free or remunerated basis, the cases in which one or the other is most desirable, the difficulties that may be encountered and the best way to avoid mistakes.

FROM THE AUTHOR'S SUMMARY.

STUDY OF WEIGHT IN INFANTS. TEODORO ZENTENO and OSCAR CORREA B., Rev. chilena de pediat. **19**:270 (March) 1948.

The authors present a comparative study of the weight at 1 year of age of a group of 49 infants at the Hospital Luis Calvo Mackenna and a group of 160 at the Caja de Seguro Obrero. The first group was composed of infants of the Asylum Service of the Hospital Luis Calvo Mackenna (a closed institution); all infants were born at full term and had normal weight at the date of hospitalization; the second group was composed of infants of Seguro Obrero polyclinics (infants of the proletariat), who were born also at term and were under pediatric care since the first weeks of life. The babies of both groups were reared by artificial feeding.

The statistical study of the material revealed the following facts:

1. The mean weight of the first group was 8,413 Gm. (± 907.18 Gm.) as compared with 8,538 (± 1,065.6) for the second group.

2. The difference between these two values is not statistically significant.

3. Under the conditions given in the study, the real mean weight of Chilean infants from the salaried class at 1 year of age should be found between 8,647 and 8,366 Gm.

FROM THE AUTHORS' SUMMARY.

DYNAMICS OF INFANT MORTALITY RATE. G. HAHN, Népegészségügy **29**:357 (June 13) 1948.

Infant mortality rate has shown a decrease to a large extent in the twentieth century; however, great differences in the amount of decrease are to be found among European countries. Infant mortality is the lowest in countries which are characterized by farming and trading and in those in which the working classes have gained real political power. The longer feudalism existed in a country, the higher infant mortality rate remained. In more socially progressive countries it is the number of fatal cases in connection with diseases of the gastrointestinal tract which falls, while the number of fatalities due to diseases of the respiratory tract, inborn weakness and childbirth mishap remains constant. There are considerable differences in infant mortality among social classes, mortality rate being much higher for the poor classes.

Special causes of decrease of infant mortality in the twentieth century are decrease of birth rate and institutional infant care. The first period in the fight against infant mortality, characterized mostly by the decrease of the number of gastrointestinal diseases, came to an end about 1930, and prenatal and home care which aim at the lowering of fatal cases in connection with inborn weakness, childbirth mishap and diseases of the respiratory tract, which were invariable for a long time, has come into prominence.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

YOUNG INFANT MORTALITY IN BUDAPEST BETWEEN 1931 AND 1943. E. FERENCZI, Orvosok lapja **4**:145 (March 7) 1948.

During the period of 1931 to 1943 infant mortality in Budapest exhibited an improvement of 16.3 per cent. In contrast to this, young infant mortality (infants less than 1 month old) remained nearly unchanged, the average being 4.1 per cent during the period mentioned. In this period 36 per cent of the infants who died were under 1 month of age. The majority of the deaths of infants aged under 1 month occurred within the first six days of life. The majority of infants who die within the first six days of life are premature, newborn infants. Thus, young infant mortality is to be combated by reduction of miscarriages.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

A BLOOD TRANSFUSION STATION OF THE PEDIATRIC CLINICS IN PRAGUE. M. MITERA, Pediat. listy, 1949, no. 1, p. 33.

The author reported on the arrangement and function of a blood transfusion station of the pediatric clinics in Prague. The station had been functioning for half a year with good results. Blood groups were examined, Rh factor was tested, blood was conserved and plasma was prepared for transfusions.

FROM THE AUTHOR'S SUMMARY.

A PLAN FOR ORGANIZATION OF THE CARE OF PREMATURE INFANTS IN THE DISTRICT. E. LUKÁSOVÁ and V. ELHENICKÁ, Pediat. listy, 1949, no. 3, p. 125.

The district institute for mothers and infants, which is concerned with the health and social preventive care of infants up to the age of 1 year, has a special unit for the care of premature infants (the number of beds is one tenth of the amount of obstetric beds). The unit is well equipped both materially and personally and has a supply of mother's milk. The district institute for public health has a special department which deals with problems of the care for premature infants in the district, especially their registration and transport. There, the district midwife is of great importance. The care for premature infants is paid by the state from a special fund, the "fight against mortality" fund.

FROM THE AUTHORS' SUMMARY.

BIRTH WEIGHTS OF FULL TERM INFANTS IN WEST CHINA. CHEN-CHIA LEE, Chinese M. J. **66**:153 (March) 1948.

A statistical study of the birth weights of 3,550 full term infants born in West China from 1938 to 1945 showed an over-all average of 3,080 Gm. The average for boys was 100 Gm. higher than that for girls.

A study was done of the factors influencing birth weight. Maternal nutrition seemed to have little influence, as there was little difference in the average birth weight in the years studied, despite the fact that the blockade deprived many of these wartime mothers of their usual quota of food. Season was influential; infants born during the winter and spring were heavier than those born in spring and summer. Both maternal age and order of pregnancy were important factors. The size of the infants increased with maternal age up to 41 to 45 years, and birth weights increased with the parity of the mother up to the seventh pregnancy.

Regional differences had influence also; infants born in West China were smaller than those born in Northern and Central China but heavier than Cantonese babies. American babies on the average were heavier than Chinese babies.

MACDONALD, Pittsburgh.

INCIDENCE OF VARIOUS DISEASES AMONG CHILDREN IN KWEICHOW. YUNG-EN KAO, Chinese M. J. **66**:487 (Sept.) 1948.

Yung-En Kao reports an analysis of the records of the outpatient department of National Kweiyang Medical College Hospital from 1939 through 1945. In this period 17,342 children were seen; of these, 5,337 were under 1 year of age. The maximum number of patients was seen in the months of June and July.

The diseases oftenest seen, in order of their frequency, are bronchopneumonia, infection of the upper respiratory tracts, diarrhea, measles, pertussis, tonsillitis, bacillary dysentery, malnutrition, typhoid and pharyngitis.

MACDONALD, Pittsburgh.

THE ALIMENTARY CONDITION OF SCHOOL CHILDREN IN THE PRIMARY SCHOOLS OF HELSINKI EXAMINED ACCORDING TO THE METHOD OF ORDER. ARMAS RUOTSALAINEN, Acta pædiat. **37**:150, 1949.

On the basis of earlier research and the experience gained in connection with it, the author concludes that measurement of a raised fold of skin provides an effective means of, for example, determining numerically the state of nourishment of school children. The method is particularly successful if combined with special evaluation tables affording a basis of definition.

FROM THE AUTHOR'S SUMMARY.

AIR CONDITIONING IN CHILDREN'S HOSPITALS. GUSTAF BIRCH-LINDGREN and A. LICHTENSTEIN, Acta pædiat. 1949, supp. 75, p. 57.

The authors emphasize the necessity of considering indirect cross infection through the air and dust and of combating cross infection by individual isolation in single rooms or cubicles. It is recommended that these units be ventilated and heated through the use of a central station air-conditioning plant, together with air-distributing ducts. Air pressure, temperature and relative humidity must be controlled. The principles for such an installation are discussed.

FROM THE AUTHORS' SUMMARY.

WEIGHT AND HEIGHT OF 30,000 SCHOOL CHILDREN IN BATAVIA. F. J. GORTER and J. H. DE HAAS, Maandschr. v. kindergeneesk. **15**:154 (May) 1947.

In this investigation 32,000 children (about 19,000 boys and about 12,000 girls) were weighed and measured. Of these children, about 21,000 were Indonesian, 6,000 European, 3,000 Chinese and 300 Arab. Difficulties were caused by the facts that not all the children in the Indies go to school and that the date of birth is not always known. In Batavia, Java, practically all the European children, half of the Indonesian boys and about a quarter of the Indonesian girls attend school. The majority of the Chinese children go to school, but only 25 per cent of these could be studied because the others go to Chinese schools.

In this investigation of school children in Batavia a selection was made according to the progress and prosperity of the non-European groups. The averages, for that reason, were somewhat higher than the actual norms. Weight and height of the children of the four Indonesian races were practically the same. The Chinese children showed a slight tendency to be larger and taller. However, there was a significant difference in weight and height between the Indonesian and Chinese school children, on the one hand, and the European children, on the other hand, the European children being taller and heavier.

At the age of 7 years Indonesian and Chinese children weigh about 18 Kg. and have a height of about 113 cm. At the age of 12 years they weigh 29 Kg. and are 134 cm. tall. The European children at 7 years weigh 21 Kg. and are 120 cm. tall and at 12 years weigh 35 Kg. and are 146 cm. tall. The average annual increase in weight of Indonesian school children is about 2¼ Kg. and the average annual increase in height is a little over 4 cm.; the average increase for European children are 3 Kg. and 5 cm.

In the Indonesian children there is but little difference according to level of prosperity, because the diets of the various prosperous groups are almost the same. For European children of various prosperity levels, however, a significant difference can be established.

This investigation shows that the Indonesian and the Chinese school child is almost two years behind in weight and height according to western criteria. This retardation dates from the second half year of life and early childhood and is increased slightly during the school years. This difference is caused by the deficiencies in nutrition. Gorter and de Haas are of the opinion that the differences in physical development among school children of different "races" in Batavia are caused primarily by differences in nutrition, especially in protein consumption, quantitative as well as qualitative, which continue over a long period.

VAN CREVELD, Amsterdam, Netherlands.

Prematurity and Congenital Deformities

GENIC FACTORS IN VISCERAL ASYMMETRY AND IN THE DEVELOPMENT AND PATHOLOGIC CHANGES OF THE LUNGS, HEART AND ABDOMINAL ORGANS. JOHAN TORGERSEN, Arch. Path. **47**:566 (June) 1949.

The purpose of this paper is to give further insight into the problem of situs inversus on the basis of a study of the genetics and the developmental genetics of this anomaly. The author made a study based on 168 cases of situs inversus. About one third of the population of Norway (1,000,000 persons) were examined by mass roentgenography. In all, about 66 per cent of the persons with situs inversus in the country were detected. The ratio of affected to normal persons does not accord with the theory that a single recessive gene is generally the cause of situs inversus. In the present material there is no evidence of an increased prenatal selection or of unknown phenotypes which may explain why the actual ratio falls short of the expected ratio in recessive inheritance. The low frequency of first cousin marriages in the familial cases and the lack of involved siblings in cases in which marriages of first cousins were noted are difficult to fit in with the theory of a single recessive gene.

There is evidence of geographic variations which parallel the variations of the frequency of twinning. This may be indication of a causal relation, but the author suggests, rather, that both may be due to independent factors, tending to be relatively common in isolated groups. The frequency of situs inversus in monozygous twins is not much higher than in the general population and situs inversus is probably rare in dizygotic twins, although the anomaly was found in both of a pair of dizygotic twins in the series studied. The mean age of mothers at the birth of children with situs inversus was found to be 31.6 years; that of mothers generally was 30.5 years.

The child with situs inversus was the only child in 13 families, the first born in 29 families and the last born in 34 families. Situs inversus is more equally distributed between sexes than cardiac defects and transposition of the great vessels. Defects of the spine and lower jaw, congenital heart disease, bronchiectasis and nasal polyps appear increased in persons with situs inversus. Anomalies of the jaw and spine may indicate inductive relations or an influence of abnormal growth rates. These findings are good evidence that the growth rates of the gills and the metameres and, accordingly, the position of the embedded vessels are of

importance in cases of asymmetry, reversal and heart defects. The relation between situs inversus and heart disease may be regarded as a clue to an understanding of the developmental process and causes of congenital heart disease. The correlation with malformations of the heart in which nongenic factors are important might indicate that nongenic factors also may be involved in situs inversus. However, the author points out that there is no case on record of situs inversus being associated with virus infection in the mother. Bronchiectasis occurred in about 25 per cent of the cases and in four of the five familial cases. The frequent coincidence of nasal polyps, bronchiectasis and small frontal sinuses in situs inversus may be regarded as good evidence of a common genic basis. The syndrome behaves as a dominant with varying expression and chance of inversion in heterozygotes and homozygotes. Evidence from morphology and genetics indicates that the asymmetry of the viscera is due to a complex of genes which may be broken up into components of particular importance in particular organs. The complete asymmetry depends on the integrative action of this complex of genes.

HAW CHAN, San Francisco.

SITUS INVERSUS WITH ASSOCIATED ABNORMALITIES. J. ROBERT JOHNSON, Arch. Surg. **58**:149 (Feb.) 1949.

Situs inversus has been known from antiquity; it is far commoner than has been generally recognized, over 1,000 cases having been recorded; it may possibly occur in the general population as often as, or even more often than, one case in 1,379 persons. It varies greatly in the number of organs involved and their degree of involvement, is frequentiy associated with other congenital anomalies and is at least as frequently associated with any acquired disease as is situs normalis. Per se, it is not incompatible with normal health. Transposition is believed to be caused by either a defect in the germ plasm or some deleterious environmental influence acting on the developing embryo.

The recognition of situs inversus can usually be made on physical examination: the heart is situated to the right of the midline; tympany of the stomach is detected on the right and dulness of the liver on the left, and in male subjects the right testicle may be more dependent than the left. Electrocardiograms and gastrointestinal roentgenograms confirm and elaborate on the diagnosis.

Three cases of total transposition of the viscera are presented, in one of which there were other skeletal anomalies, namely, a cervical rib and spina bifida occulta.

FROM THE AUTHOR'S SUMMARY.

ENCAPSULATED DEAD FETUS IN THE PERITONEUM. P. N. RAJU and P. RAMA RAO, J. Indian M. A. **17**:299 (June) 1948.

In a case in which there were fever and abdominal pain, with a large mass in the left iliac fossa, and encapsulated dead fetus, apparently the result of a tubal pregnancy, was found. The fetus appeared to be 29 weeks old.

McGUIGAN, Evanston, Ill.

CLINICAL AND PATHOLOGICAL ROLE OF *d,l*-ALPHA TOCOPHEROL IN PREMATURE INFANTS: STUDIES ON THE TREATMENT OF SCLEREDEMA. F. GERLOCZY, Ann. pædiat. **173**:171 (Sept.) 1949.

Classification, differentiation, pathology and etiology of sclerema are discussed. The author states that the disease occurs more frequently in premature babies weighing over 1,500 Gm. and that the number of cases is increasing. Premature babies in whom scleredema develops have a much worse prognosis than premature ones without scleredema.

There is no reference in the literature to vitamin E therapy in scleredema. The investigations of the author were prompted by the clinical observation of castastrophic diuresis and loss of weight in an infant treated for scleredema with vitamin E.

The results of earlier investigations are summarized. Vitamin E invariably produced severe diuresis. When given intramuscularly it had no effect. A cautious dosage was used to prevent loss of body weight: for two days 5 mg. daily were given orally. When the result was

unsatisfactory, namely, if no diuresis or loss of weight occurred, the same dosage was continued for not more than five days. Urinary output and body weight were carefully observed. The results were good.

The later prognosis of the infants treated with vitamin E is favorable.

The poor prognosis is due to the edema of the vitally important internal organs. Scleredema is merely a partial phenomenon of general edema. The presence of scleredema is indicative of visceral edema. Vitamin E exerts a draining action on visceral edema and scleredema alike, and it is because of this effect that the prognosis is improved. This assumption has received much support by animal experiments and by some corroborating data from human pathology.

Scleredema mainly occurs on the second or third day of life. At this age the newborn infant is very sensitive to vitamin E and diuresis occurs. The later vitamin E is administered the less effect it has in draining the patient. Vitamin E has no effect in mature and premature infants without scleredema.

Great precaution has to be taken in administering vitamin E to infants with scleredema. No other kind of fluid accumulation can be mobilized by vitamin E, enormously high as its dose appears to be. Apart from the scleredema, the danger from overdosage is nil.

Scleredema can, after the onset of milk secretion, be cured by giving vitamin E to the mother only.

In none of the infants given 5 mg. of tocopherol a day preventively from the first day of life did scleredema develop.

FROM THE AUTHOR'S SUMMARY.

AN ENCEPHALO-OPHTHALMIC SYNDROME IN TWO PREMATURE CHILDREN: A CLINICAL STUDY. J. HENNING MAGNUSSON, Ann. pædiat. **173**:246 (Oct.) 1949.

An account is given of an encephalo-ophthalmic syndrome in two extremely premature children. The first patient was born just over three months before term, weighing 1,170 Gm.; the other was a dizygotic twin born six weeks before term, weighing 1,180 Gm. In both cases attention was focused on the pathological conditions, on the grounds of ophthalmic lesions. These were first observed at the age of 2½ and 3½ months respectively. In neither case could any retinal function be demonstrated with the help of electroretinography. The mental development was retarded and cerebral lesions were demonstrated in both cases by means of ventriculography and electroencephalography.

FROM THE AUTHOR'S SUMMARY.

A CASE OF FAMILIAL FUNCTIONAL DIENCEPHALOHYPOPHYSIAL SYNDROME WITH DWARFISM, INFANTILISM, GLYCOGENOSIS AND LIPEMIA. E. ZIEGLER, Helvet. paediat. acta **2**:56 (Jan.) 1947.

Ziegler reports a case of hereditary diencephalic pituitary syndrome with dwarfism, acromicria, hypogenitalism and infantilism connected with glycogenosis (von Gierke's syndrome with hepatomegaly and nephromegaly), a marked increase in lipemia, hyperproteinemia and dysproteinemia. In the development of this disease, there appeared a serious syndrome of the hepatorenal system with damage to the liver parenchyma and nephrosis, recurrent infection of the urinary tract and, finally, beginning renal deficiency. Intermittent hemorrhagic diathesis and progressive anemia also appeared. Death occurred at the age of 23 years. Autopsy showed that the liver contained large adenomas and a considerable amount of fatty infiltration with characteristic glycogenosis; the kidney also exhibited glycogenosis. Lipemia was recognizable histologically in the organs; pseudofat emboli, in the lungs. Clinically there seemed to be too litttle pituitary secretion, but histological examination of the pituitary gland and hypothalamus did not show any pathological condition. Two half-sisters were affected, but since the two parents other than the common parent had no consanguinity, the disease could not be shown to be transmitted by a recessive hereditary character.

FROM THE AUTHOR'S SUMMARY.

THE ACTION OF BETA PHENYLISOPROPYLAMINE AND OF CAFFEINE ON IMMATURE INFANTS. A. MALAGUTI, Clin. Pediat. **31**:159 (March) 1949.

Immature infants frequently will go to sleep at the breast and thus present definite problems of failure to gain in weight and failure to maintain the supply of breast milk in the mother.

Twenty such babies were given either coffee or beta phenylisopropylamine (an ephedrine-like compound) or both, with very satisfactory results in prolonging the duration of a nursing period and very satisfactory gains in weight. The daily amount of coffee given was 4 teaspoonfuls (25 mg. caffeine) and of beta phenylisopropylamine, 1.25 mg. These amounts were divided into four parts, one part being given 30 minutes before each of the day's first four feedings.

HIGGINS, Boston.

SOME CLINICAL-STATISTICAL DATA ON FETAL MALFORMATIONS. P. SPOTO, Lattante **18**:338 (June) 1947.

Spoto studied the relation between maternal illness and congenital malformations in newborn infants from data obtained from records of the Obstetrical Clinic of the University of Parma. In the period from Nov. 1, 1938 to June 30, 1947 there were 8,228 births in the clinic; of this group, 68 of the mothers gave birth to 70 infants with congenital malformations. The number of malformed infants did not appear to be related to the war.

The following malformations were found: anencephaly, 12; hydrocephalus, 8; spina bifida, 5; multiple hemangiomas, 2; cleft palate, 5; epispadias, hypospadias and extrophy of bladder, 4; abdominal fissures, 5; club feet, 10; osteogenesis imperfecta, 3; polydactyly, syndactyly and adactyly, 7; and other malformations, 9. The total number of malformation cases was 70.

Fourteen of the cases were associated with a maternal illness; the illnesses found to be involved were syphilis, tuberculosis, blood disease, jaundice, toxemia of pregnancy and intense sympathetic contonia, but not rubella. The frequency of malformation was slightly higher in infants of unmarried mothers (1 per cent) than in infants of married mothers (0.8 per cent). Malformations were most frequent in primipara, next in pluripara and least frequent in secundipara mothers. One of twins was malformed in five cases and both twins in two cases; thiry-nine of the malformations were in males and 31 were in females. Clubbed feet was more common in males, and anencephaly and hydrocephalus, in females. Seventeen of the infants were stillborn and 30 were immature.

HIGGINS, Boston.

SUPERNUMERARY NIPPLES IN CHILDREN. L. GAMBARA, Lattante **18**:370 (June) 1947.

Observations made on about 10,000 children revealed 37 children with supernumerary nipples; 23 were boys and 14 were girls. The accessory nipple was on the right side only in 8 children (all boys) and on the left side only in 24 children (14 boys and 10 girls) and in 5 children (1 boy and 4 girls) there was one accessory nipple on each side. In no cases were more than two accessory nipples found.

HIGGINS, Boston.

CONGENITAL FAMILIAL ELEPHANTIASIS (MILROY'S DISEASE). GOFFREDO FROLA, Pediatria **56**:726 (Oct.-Dec.) 1948.

The author gives a description of two cases of congenital familial elephantiasis of the feet. The histological examination showed the presence of a matrix of fibrous connective tissue, in the interstices of which the characteristic dilated lymphatic vessels were locked. A review of the subject is given, and the prospect of the actual classification of the congenital hypertrophies is discussed.

FROM THE AUTHOR'S SUMMARY.

STATUS BONNEVIE-ULLRICH. GIAN CARLO MORANDO, Pediatria **56**:746 (Oct.-Dec.) 1948.

The author describes a case of "Status Bonnevie-Ullrich" that he was able to observe. This syndrome consists of outstanding deformities all shown by the same patient: pterygium colli, dwarfism, infantilism, mental deterioration, mammary hypoplasia and skeletal anomalies.

The above is the second case so far reported in Italy.

FROM THE AUTHOR'S SUMMARY.

CONTRIBUTION TO THE KLIPPEL-FEIL SYNDROME. WOLFGANG HERZOG, Med. Klin. **44**:1221 (Sept. 23) 1949.

The Klippel-Feil syndrome was diagnosed in a 49 year old woman. A synostosis of the four upper cervical vertebrae was combined with a left-sided cervical rib and absence of the

twelfth ribs. Neither a cervical spina bifida nor a basal impression of the skull could be demonstrated by roentgenogram. It is concluded that there is no disease *sui generis*, but that the syndrome is one manifestation of an ontogenetic dystrophy.

AMBERG, Rochester, Minn.

CONGENITAL PARTIAL GIGANTISM. BURKHART SACHS, Ztschr. f. Kinderh. **66**:36, 1948.

The author describes six cases of partial congenital gigantism affecting, respectively, one leg, one hand and one leg, one side of the body, the first, second and third finger of one hand, the first and second finger of one hand, and the head and neck.

Issue is taken with the differentiation between congenital and secondarily acquired forms of gigantism due to various pathological processes. Coexisting malformations, such as syndactylism, polydactylism, clubfoot, malformations of the skin, lipomas, exostoses and heart lesions, are frequently found and were present in the six cases reported in the article. The occurrence of coexisting malformations as reported in the literature is tabulated, and it is statistically proved that their occurrence is by far more frequent in patients with gigantism than in the general population. Etiologically the author considers mechanical, neurogenic, vascular and embryologic disturbances, as well as hereditary factors. He feels that the two last-mentioned factors are most likely of etiological importance.

GLASER, Chicago

PROVISION FOR CHILDREN BORN WITH HARELIPS AND CLEFT PALATE. A. BERNDORFER, Népegészségügy **29**:504 (Aug. 29) 1948.

Children with harelips and cleft palate are born everywhere. Owing to various causes they are not always presented to general practitioners or specialists. The people must be enlightened that a child born with this defect can be successfully operated on and become quite normal. However, operative intervention alone is not sufficient; the defect of the speech must be corrected by competent teachers who have the necessary medical knowledge. The whole problem may be solved by a central directing organ.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

THE KLIPPEL-FEIL SYNDROME. G. LENÁRT, Orvosok lapja **4**:1029 (Aug. 8) 1948.

The author reports a case of a 3 year old boy rather retarded in his bodily development; the head was held rigidly and there was almost no neck, and the motion of the shoulder girdle was limited. The roentgenogram showed that from the seventh cervical to the fifth thoracic vertebra there was complete congenital malformation, with deformed supernumerary vertebrae, spina bifida, costal malformations and the like. Since the relatives of the boy were living abroad, the hereditary relation could not be investigated.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

SCLEREDEMA OF PREMATURE INFANTS, A DEFICIENCY DISEASE. F. GERLÓCZY, Pædiat. danub. **5**:169 (March-April) 1949.

The incidence of scleredema had been significantly increasing from 1945 to 1948. It is a clinical entity which can be sharply differentiated from other edematous processes appearing in premature infants. It disappears within two to three days after peroral administration of racemic alpha tocopherol acetate. Caution is indicated in the dosage of the drug, as pathological loss of water may follow large doses. Vitamin E, apart from producing the disappearance of scleredema, also ensures amelioration of the prognosis of premature babies. The bad prognosis of infants suffering from scleredema is due to latent edemas, which are also lost after vitamin E medication.

FROM THE AUTHOR'S SUMMARY.

SCLERODEMA IN PREMATURE INFANTS. F. GERLÓCZY, Pædiat. danub. **6**:90 (Aug.) 1949.

Scleredema, the incidence of which has been significantly increasing in premature infants in the postwar years, is probably due to deficiency in vitamin E. Oral administration of

racemic alpha tocopherol acetate makes the condition disappear, with increased diuresis and loss of fluid, within two to three days. Daily doses of 5 mg. for two to five days seem to cause no harm. The prognosis of infants suffering from scleredema is greatly ameliorated by vitamin E treatment. The unfavorable mortality rate of infants not treated with vitamin E is due to edema of the inner organs. Since the end of 1948 the number of scleredema cases has been constantly decreasing. At the same time their prognosis, in spite of their treatment with vitamin E, has become unfavorable again.

FROM THE AUTHOR'S SUMMARY.

A CASE OF HYPERPLASIA AND A NEW THEORY ABOUT THE FORMATION OF CONGENITAL MALFORMATION. DOROTA GRÉGROVÁ, Pediat. listy, 1949, no. 3, p. 110.

The author describes a case of hyperplasia of the second and third toe of the right foot, with a large hemangioma on the right gluteal region, the thigh and the shank of a 4 month old boy. New theories on the formation of congenital malformations are discussed.

FROM THE AUTHOR'S SUMMARY.

THE DEVELOPMENT AND FUTURE OF PREMATURE CHILDREN. KORNEL CHMELO and ELENA FURDIKOVA, Pediat. listy **4**:156, 1949.

On the basis of observation of the further development of 35 of a group of 300 premature children found, the authors conclude that premature children are equal to other children in their later life.

FROM THE AUTHORS' SUMMARY.

MENTAL DISTURBANCES IN PREMATURE CHILDREN AT SCHOOL AGE. BERNHARD BESKOW, Acta pædiat. **37**:125, 1949.

A group of 273 premature children were tested for I. Q. in a follow-up study when they were between 9 and 15 years of age; 16.11 per cent had I. Q.'s below 85. Those children who had had cerebral hemorrhages during the first postnatal period (6.59 per cent) had experienced the greatest difficulty in getting on at school and had the lowest I. Q.'s. On the average the children had commenced to walk and talk later than children belonging to an unselected control group, and they were likewise inferior to normal children in their mental development. When data from those who had suffered postnatal hemorrhages of the brain or cyanotic attacks and those whose parents were mentally deficient were left out of account, however, it was found that development was normal. One half of the children who had had cerebral hemorrhages showed spastic paresis at school. About 50 per cent of the children in the group had nervous symptoms (in a control group taken at random the figure was about 30 per cent). Children who have suffered cyanotic attacks behave like those who have had cerebral hemorrhages. If these cases are left out of consideration, it is found that premature children develop like normal ones, although they have nervous disorders to a greater extent than the latter.

FROM THE AUTHOR'S SUMMARY.

ARTHROGRYPOSIS MULTIPLEX CONGENITA. D. P. R. KEIZER, Maandschr. v. kindergeneesk. **17**:92, 1949.

The author gives a description of the occurrence of arthrogryposis multiplex congenita in a boy of 11 years who had signs of status dysraphicus, hypocorticalism, sexual infantilism and debilitas mentis.

FROM THE AUTHOR'S SUMMARY.

Newborn

NUTRITION STUDIES DURING PREGNANCY: V. RELATION OF MATERNAL NUTRITION TO CONDITION OF INFANT AT BIRTH; STUDY OF SIBLINGS. BERTHA S. BURKE, STUART S. STEVENSON, JANE WORCHESTER and HAROLD C. STUART, J. Nutrition **38**:453 (Aug. 10) 1949.

A study of the physical condition at birth of 68 siblings (57 second, 10 third siblings and 1 fourth sibling) born to 57 of the women studied in a previously published series of cases

has been made by Burke and others in relation to the mean general dietary rating for the latter part of these subsequent pregnancies.

In the 284 cases, when the maternal diet was "excellent or good," 95 per cent of the infants were in good or excellent physical condition at birth and only 5 per cent were in either fair or poorest physical condition. In contrast, when the maternal diet was "poor to very poor" 65 per cent of the infants were in the poorest physical condition at birth and 27 per cent were in fair condition, whereas only 8 per cent were in either good or excellent physical condition. A "very poor" maternal diet is associated with an infant in the poorest physical condition at birth, whereas an "excellent or good" diet is associated with an infant in excellent or good condition at birth. All the stillborn infants, all the neonatal deaths but one, all the premature infants but one (a neonatal death), all the functionally immature infants and most of the congenital defects were found in the group of infants born to mothers with "poor or very poor" prenatal diets. Since no major effort was made to change the dietary habits of these women, it is probable that in the majority of the cases the prenatal dietary rating was representative also of long-time food habits. The average birth weight and birth length of the infant decreased as the maternal dietary rating became poorer.

Data were presented on 53 matched pairs of siblings. Improvement of the infant's condition with improvement of the maternal diet and deterioration of the infant's condition with deterioration of the maternal diet appeared in this series in which each of the 53 mothers was observed through two pregnancies. While the changes were not sufficiently striking to be statistically significant, it is felt that this series of matched siblings is unique, since it has been possible to use each mother as her own control and thus in part minimize hereditary and environmental variables which influence the condition of babies at birth.

FREDEEN, Kansas City, Mo.

EPIDEMIC DIARRHEA OF THE NEWBORN INFANT. JAMES G. CUMMING, J. Pediat. **34**:711 (June) 1949.

Epidemic diarrhea in newborn nurseries may be traced to bacterial contamination of the formula or to contact infection. Cumming suggests that the formula may be protected from contamination by the following technic:

1. Autoclave all equipment including the nipples. Protect the nipples in the container by wrapping them in toweling.

2. Autoclave formula stock water, cool it to room temperature and chill overnight in the refrigerator.

3. Refrigerator temperature should be set at 40 to 45 F. and should never go above 50 F. Temperature should be recorded at 9 a. m. and 1 p. m.

4. Limit formula nurses' duties to the preparation of not more than three different formulas.

5. Prepare and bottle food according to good aseptic technic. Culture six to ten 24-hour formulas to check the effectiveness of the technic.

6. Bacterial counts of 24-hour formulas should not be more than 500 per cubic centimeter, and no single count should be more than 10,000. Counts over 100,000 are a danger signal.

The recent procedure of autoclaving bottled food by the high pressure-low temperature method will sterilize 99 per cent of the formulas.

MACDONALD, Pittsburgh.

INTELLIGENCE QUOTIENT OF CHILDREN WHO HAVE RECOVERED FROM ERYTHROBLASTOSIS FETALIS. JOAN M. GERVER and RICHARD DAY, J. Pediat. **36**:342 (March) 1950.

Children who have recovered from erythroblastosis fetalis without obvious motor nerve damage have lower intelligence quotients than those of their unaffected older siblings. The difference is slight but significant. Gerver and Day observe that this effect is not necessarily specific but is, perhaps, the result of any severe neonatal illness. They also point out that the extent of the impairment is so mild that there is no reason for altering the good prognosis usually given to the parents of the child who has recovered from erythroblastosis without suffering motor nerve injury.

MACDONALD, Pittsburgh.

USE OF DIETHYLSTILBESTROL TO PREVENT FETAL LOSS FROM COMPLICATIONS OF LATE PREGNANCY. O. WATKINS SMITH and GEORGE VAN S. SMITH, New England J. Med. **241**:562 (Oct. 13) 1949.

The progress and outcome of pregnancy in 180 women to whom diethylstilbestrol U. S. P. (stilbestrol®) was administered for the prevention of late pregnancy complications are reported. The authors elucidate their reasons for the use of this drug in pregnancy and analyze the results statistically, comparing the patients' courses and outcomes of delivery while taking diethylstilbestrol U. S. P. to their previous obstetric history.

The figures given are complex, and the article should be read by pediatricians and obstetricians who are interested.

WHEELOCK, Denver.

ETIOLOGIC FACTORS IN TETANY OF NEWBORN. LYTT I. GARDNER, E. A. MACLACHLAN, W. PICK, M. L. TERRY and A. M. BUTLER, Pediatrics **5**:228 (Feb.) 1950.

The cases of 16 infants with neonatal tetany are reported, all of whom were fed cow's milk formulas.

Relative to human milk, cow's milk has a low calcium-phosphorus ratio and increased total phosphorus concentration. These differences are accentuated in some commercial milks prepared for infant feeding. Cow's milk, even if diluted 2:1 with water, is an unphysiological food for the human infant in the neonatal period, producing elevated serum phosphorus and decreased serum calcium and magnesium levels. Increasing the calcium-phosphorus ratio of cow's milk to that of human milk or diluting 1:2 with water limits the abnormal changes in serum phosphorus, calcium and magnesium concentrations referred to above.

A high phosphorus diet of an inadequately diluted cow's milk formula causes hypertrophy of the parathyroid glands of the newborn infant. The maximum renal phosphorus clearance of the newborn in the first week of life appears to approximate 3,500 milliliters per square meter surface area a 24-hour period. Our observations indicate that when newborn infants are fed cow's milk formulas commonly used in this country, limitation in parathyroid and renal function predisposes them to tetany.

The foregoing data emphasize the physiological character of human milk for the newborn infant. If breast milk is unavaliable, a suitable formula for the neonatal period appears to be cow's milk 1 part, water 2 parts, 10 per cent carbohydrate and calcium gluconate to produce a calcium-phosphorus ratio approaching that of breast milk. The amount of added water and calcium should then be gradually reduced.

FROM THE AUTHORS' SUMMARY.

TREATMENT OF ERYTHROBLASTOSIS: ANALYSIS OF COMMUNITY EFFORTS USING THE SUBSTITUTION TRANSFUSION. CLEMENT J. MOLONY, Pediatrics **5**:1008 (June) 1950.

The first two years' experience with the substitution transfusion in the Los Angeles area is reported and analyzed. Forty-five patients received this treatment. Results of therapy are compared with the results in 35 patients studied at the Los Angeles Childrens Hospital during the same period who were not treated with substitution transfusions.

Mortality figures favored the use of the conservative, multiple simple transfusion method of treatment in the series reported. Even in groups with comparably severe erythroblastosis, the patients receiving the substitution transfusions showed a higher mortality. Evidence is presented demonstrating that errors in technic may have had an appreciable effect on the poor showing made by the substitution transfusion method of therapy. However, such errors may be inherent in any radical procedure. The series of cases is analyzed as to mortality, development of kernicterus, effect of previous pregnancies, effect of previous siblings with erythroblastosis, effect of transfusions, correlation of Coomb's test with severity of disease, correlation of maternal antibody titer with severity of disease, number of transfusions needed for a cure and legnth of stay in the hospital.

An objective standard to measure the severity of an individual case is suggested. Although empirical, it allows for summations and resolves a case down to a numeric figure. Thus the case can be compared to other cases in an analysis of any phase of the disease.

Use of Coomb's (or antiglobulin) test is described. This test was found to be reliable, easy to perform and extremely sensitive. There was a good correlation between the strength

of the test and the severity of a case. Substitution transfusions were not performed unless the results of the test were positive.

Errors in performing the substitution transfusion are described. These errors include using too little blood, delaying the operation too long, giving blood into the umbilical vein, injecting calcium improperly and failing to protect the infant against exposure and dehydration.

A technic for the substitution transfusion is presented in detail with suggestions to avoid the errors made in these cases. The theoretical advantages inherent in the substitution transfusion are enumerated.

FROM THE AUTHOR'S SUMMARY.

A DISEASE PICTURE SIMILAR TO HEMOLYTIC DISEASE PRODUCED BY HETEROSPECIFIC N. C. GASSER and A. GRUMBACH, Helvet. paediat. acta **4**:54 (Feb.) 1949.

A case is described resembling icterus gravis with congruity of the Rhesus and ABO systems but incompatibility of the MN system. In the third week after the birth, glutinins against the fetal N were found in the mother's blood; they disappeared in the second month. On account of increasing anemia, transfusion of Rh, ABO and MN compatible blood was given, which gave rise to an incompatibility reaction, possibly as a result of the maternal antibodies still circulating in the child's blood. The existing literature on MN incompatibility is briefly discussed.

FROM THE AUTHORS' SUMMARY.

MISTAKEN DIAGNOSIS: BILIARY ATRESIA; ICTERUS GRAVIS NEONATORUM. H. OPITZ, Kinderärztl. Praxis **16**:73 (March-April) 1948.

The case of a newborn infant with the following findings is described: jaundice on the second day of life and anemia with 5 erythroblasts per 100 leukocytes, positive reaction of the urine for bilirubin and urobilinogen, positive results in van den Bergh's indirect test and slightly positive results in the direct test, normal stools and hemorrhages in skin and umbilical cord. The mother and father and a 7 year old sibling were well. The referring doctor's diagnosis was obstruction of the bile ducts. On admission to the hospital the baby was taken off mother's milk and was given Rh-negative transfusions and vitamin K. The child improved rapidly.

In differentiating obstructive and hemolytic jaundice in the newborn, it has to be considered that in the former the stools may not be alcoholic during the first days and that in the latter they may become light in the course of the disease. The greenish color of the skin may occur in both conditions. The presence of urobilin in the urine speaks for a hemolytic process, but bilirubin, ordinarily found in obstructive jaundice, may also be present in severe hemolytic processes owing to the inability of the liver to handle the excess bilirubin.

Further investigation of this case proved the mother to be Rh negative, the father and child Rh positive. The mother's blood showed the presence of Rh agglutinins. The mother's breast milk showed no agglutinins but did show blocking antibodies. Opitz points out the difficulty of differential diagnosis of the two causes of jaundice; he briefly considers syphilis and septicemia as possible causes and emphasizes the need for an investigation of the family history and blood group determination in the parents and child. He remarks about the unusually long interval between the sensitization of the mother by her first child (seven years prior) and the birth of this child, with no other pregnancies or transfusions in the interval.

GLASSER, Chicago

ATYPICAL CLINICAL OBSERVATIONS IN CASES OF FAMILIAR ERYTHROBLASTOSIS AND THEIR SEROLOGIC EXPLANATION ACCORDING TO THE THEORY OF LEVINE. P. DAHR and H. KNÜPPEL, Med. Klin. **44**:726 (June 10) 1949.

Attention is called to cases in which three or more healthy infants were born although the mother was Rh negative while the father was Rh positive. In such a family five Rh-positive children were normal, while the four next ones had icterus gravis. Examples are also cited in which an Rh-positive father and an Rh-negative mother had a normal infant after previous erythroblastotic ones when the father was heterozygous and the infant Rh negative. Another observation of a first child being erythroblastotic could be explained by previous transfusions the Rh-negative mother had received from the Rh-positive father.

AMBERG, Rochester, Minn.

SOME CONSIDERATIONS CONCERNING THE ORIGIN OF RH CONDITIONED DISTURBANCES ON TRANSFUSION. PETER DAHR, Med. Klin. **44**:1212 (Sept. 23) 1949.

An Rh-negative wife with an Rh-positive husband had stillborn hydropic children. Both parents belonged to group O. In the blood of the wife no Rh antibodies of any kind could be demonstrated after a period of about three years. The results of cross tests with the husband's blood were entirely negative. After an intravenous injection of 5 milliliters of the husband's citrated blood it was possible to demonstrate antibodies in the wife's blood in two days, first only in traces. Four months later she received again 2 milliliters. Before this injection no antibodies were present. They appeared the day following the injection. After both injections slight fever and some subjective symptoms were noted. The probable explanation is a rapid formation of antibodies.

AMBERG, Rochester, Minn.

CARE OF THE NEWBORN IN HUNGARY. L. DOBSZAY, Népegészségügy **29**:721 (Dec. 19) 1948.

By far the greater part of deliveries takes place at home without any medical assistance in Hungary (80 per cent outside of Budapest); thus the handling of newborn nursing is practically in the hands of the midwives. Experience shows that a great many of even the well qualified midwives do not live up to the requirements. There is a lack in their education, practical training and control. The low cultural and social standard of country people of Hungary adds to the difficulties in the case of the newborn. The maternity homes of the public health service in villages are of great importance. Their building and maintenance are relatively cheap. They are easily accessible, and thus they prove very efficient. Initial steps were taken for the establishment of modern separate wards for the newborn. Such wards show excellent results. It is necessary to use these experiences in the course of the work of rebuilding and modernization.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

THE INFLUENCE OF POTASSIUM ON THE PHYSIOLOGICAL WEIGHT LOSS OF NEWBORN INFANTS. L. BARTA and I. JENEY, Paediat. danub. **5**:11 (Jan.) 1949.

The authors gave newborn infants 50 to 100 milliliters daily of a solution containing potassium chloride 0 to 3 Gm., sodium chloride 0 to 5 Gm. and dextrose 10 Gm. per 100 milliliters and in addition intramuscular injections of 3 to 6 milliliters of a 10 per cent calcium gluconate solution once or twice daily. This treatment was given for the first four days.

In over 50 per cent of all infants either no loss of weight occurred or it was less than 50 Gm. In the vast majority of infants the birth weight was regained within six days.

The combination of potassium with aminosol® may be of value, but its administration is often prevented by the infant's vomiting. Desoxycorticosterone acetate (percorten®) as well as potassium should be given to premature infants. The simultaneous administration of potassium and calcium exerts a favorable influence on the course of icterus neonatorum.

FROM THE AUTHORS' SUMMARY.

HEMOLYTIC DISEASE OF THE NEWBORN. J. POZSONYI, Paediat. danub. **6**:27 (July) 1949.

An unusual sequence of events in a family is reported. An Rh-negative mother whose husband was Rh-positive had eight pregnancies. The first five children died soon after delivery, while three subsequent children remained alive. All the three living children are Rh-positive. The sixth child is healthy; the seventh suffers from athetosis and oligophrenia, probably in consequence of kernicterus; the eighth child is healthy.

Contrary to the rule that the later the Rh-positive pregnancy of an Rh-negative mother, the more antibodies will be developed and the more the fetus will be damaged, it was the children born later who were fit to live.

FROM THE AUTHOR'S SUMMARY.

RH FACTOR AND A PRELIMINARY REPORT ON RH TESTS IN CHINESE. WEI-LIANG YU, Chinese M. J. **66**:453 (Aug.) 1948.

Two hundred and eighteen Chinese were tested for the Rh factor. One (0.4 per cent) was Rh negative.

MACDONALD, Pittsburgh.

ON PROPHYLACTIC AND EARLY TREATMENT OF INFECTIONS IN NEWBORN INFANTS, ESPECIALLY THE PREMATURE. GRETA MUHL, Acta paediat. **37**:221, 1949.

Neonatal infections among children transferred from the maternity department of the Malmö General Hospital to the Flensburg Children's Hospital during the last four to five years have increased considerably, doubtless because of difficulties in affording ward accommodation and procuring a suitable nursing staff.

To neutralize to some extent the dangers that threaten the newborn, we at the Children's Hospital have directed our efforts toward early diagnosis and treatment of these infections. We have found determination of the white blood corpuscles of benefit, inasmuch as these, especially the polymorphonuclear cells, often increase before clinical symptoms appear. In many cases leukocyte counts have enabled us to commence treatment earlier than would have been possible otherwise.

However, since premature and diseased children are usually not transferred to the Children's Hospital until the fifth to seventh day of life, for the past nine months we have conducted prophylactic treatment of infants especially disposed to infections (viz. the asphytic, those who aspirate and those lethargic after cerebral injuries or other parturient lesions) in the maternity department. It is these children who are prone to contract the early diseases of the lungs which in this as well as other studies appear to dominate among the neonatal infections. This category of specially threatened children should also embrace the very small infants with birth weights under 1,500 Gm., as these have been proved to belong to the specially delicate class.

The results obtained have been encouraging. The mortality among the infected infants has dropped from 78.5 per cent during 1944 to 37.5, 22.2, 15.8 and 14.3 per cent respectively during the subsequent years.

FROM THE AUTHOR'S SUMMARY.

Acute Contagious Diseases

ENCEPHALOMYELITIS COMPLICATING MEASLES: A CLINICAL AND ELECTROENCEPHALOGRAPHIC STUDY. ERIK JACOBSSON and BÖRJE HOLMGREN, Ann pædiat. **173**:231 (Oct.) 1949.

Encephalomeningites complicating measles as well as other virus infections have during recent years shown an augmented frequency. The etiology is obscure, but a number of theories have been advanced, the two most important being, first, the theory of activation by an unknown neurotropic virus, and second, the theory of the specific virus of the primary disease. On the basis of the symptom picture in 46 cases of this disease treated at the Hospital for Infectious Diseases in Stockholm since 1925, and of the information gained from the approximately 350 cases published to date, a survey of the clinical course of the disease is made. The comparatively frequent occurrence of paresis of the bladder in the acute stage in our own patients is striking. The mortality rate is high. For the surviving patients the prognosis is comparatively good, although it is questionable for the patients with more severe disease. Therapeutic measures are discussed.

Twelve of 14 patients with encephalitis and four with uncomplicated cases of measles from the latest epidemic have been examined once or several times with electroencephalography. A tabulation of the electroencephalogram findings is presented in which it is clearly revealed that in the majority of the cases an abnormal electroencephalogram is shown in the acute stage, this, however, relatively soon becoming normalized. The more severely affected patients, especially those with cramps, show long-standing electroencephalogram changes.

The pathologicoanatomic findings are reported briefly.

FROM THE AUTHORS' SUMMARY.

PROPHYLAXIS BY PENICILLIN FOR CARRIERS OF THE DIPHTHERIA BACILLUS. C. TORRICELLI and A. MONTAGNA, Lattante **18**:474 (Aug.) 1947.

Twenty-two children, carriers of Corynebacterium diphtheriae, were treated with local applications of penicillin (1,000 units per cubic centimeter) four to six times daily; four to fifteen days later cultures were negative for the bacilli.

In vitro, 1 unit of penicillin per cubic centimeter was bacteriocidal and higher dilutions were bacteriostatic for diphtheria bacilli. In no instance did the penicillin change a toxin-producing

diphtheria bacillus to a nontoxin-producing bacillus. Most of the strains of C. diphtheriae found in the carriers were not toxic to guinea pigs.

HIGGINS, Boston.

TREATMENT OF PERTUSSIS BY LOWERED BAROMETRIC PRESSURE AND BY THE GIVING OF ACID. E. COMOLLI, Lattante **18**:513 (Sept.) 1947.

One hundred and fifty children with pertussis were placed in a decompression chamber five times on alternate days; the barometric pressure was lowered to the equivalent of an altitude of 4,000 meters over a period of fifteen to twenty minutes, was maintained at this level for twenty minutes and was then allowed to return to normal gradually in twelve to twenty minutes. Excellent and immediate relief from the symptoms of whooping cough was obtained in 45 cases; some beneficial results occurred in another 73 cases, and there was no improvement in 33 cases. Good results were more frequent for infants under 1 year of age (89 per cent) than for children 1 to 4 years old (80 per cent) and children 4 to 10 years old (67 per cent).

Since high altitudes result in mild acidosis, and since severe coughing may result in hypocapnia, acid therapy in pertussis seemed logical. Therefore, 974 children with pertussis were given acid-producing therapy, either ammonium chloride, calcium chloride, monosodium phosphate and ascorbic acid or a lemonade containing hydrochloric acid. This method of treatment gave beneficial results in 70 per cent of all cases and in 81 per cent of the cases of infants under 1 year of age. The probable mechanism of the relief of symptoms is discussed.

These methods of treatment are more adaptable to general use than the practice of taking the children on airplane trips.

HIGGINS, Boston.

NEW PERCUTANEOUS METHOD FOR SMALLPOX VACCINATION. L. MORO and U. GIURANNA, Lattante **2**:42 (Jan.) 1950.

Ten per cent sodium hydroxide was rubbed on a small area of skin by a probe tipped with cotton; this produced sufficient erosion to cause takes in 20 children when smallpox vaccine was then applied to this area. The claim is made that this method is less disturbing to the child and that there is less chance of local infection.

HIGGINS, Boston.

NONSPECIFIC INTRADERMAL VACCINE THERAPY IN THE SEQUELAE OF HEINE-MEDIN DISEASE. B. CARLETTI and S. NASSO, Minerva pediat. **2**:1 (Jan.) 1950.

Acqua reported improvement in patients with paralysis from poliomyelitis following administration of a vaccine made from cultures of bacteria from the patient's nasopharynx and rectum. Carletti and Nasso treated 242 paralytic patients with poliomyelitis in the same way except that a stock vaccine was used; the vaccine contained 11 throat and fecal bacteria, including Escherichia coli, Salmonella paratyphosa A and B, enterococci, Streptococcus pyogenes, Hemophilus influenzae, pneumococci, and Micrococcus catarrhalis. Twenty injections were given intradermally in increasing doses spaced at intervals of four to seven days; the spacing was such as to allow for the subsidence of the local reaction from the previous injection. Then a rest period of two to three months was followed by another series of injections.

The authors felt that beneficial results followed this procedure in 51 per cent of the patients paralyzed less than one year and in 31 per cent of the patients paralyzed over one year; no improvement was obtained in 18 per cent of the patients.

HIGGINS, Boston.

MENINGOENCEPHALITIS IN EPIDEMIC PAROTITIS IN CHILDREN. I. V. VOVNIANKO, Pediatria, 17, January-February, 1949.

Eleven cases of epidemic parotitis with severe involvement of the central nervous system are presented. The following are the author's main conclusions. 1. Meningoencephalitis is not an uncommon complication of epidemic parotitis in children. 2. Cerebral manifestations may occur at any stage of the parotid gland involvement, that is, prior to the appearance of obvious swelling, coincident with it or after its disappearance. 3. Meningoencephalitis occurs frequently in association with pancreatitis in epidemic parotitis among children. 4. The clinical

picture of cerebral involvement in epidemic parotitis is characterized by signs of an acute serolymphocytic meningitis or meningoencephalitis of stormy course. 5. The sudden onset with high fever and early signs of involvement of the central nervous system frequently accompanied with abdominal distention and pain should permit an early diagnosis of mumps meningoencephalitis and early isolation of the patient. 6. The treatment of mumps meningoencephalitis is still purely symptomatic. The prognosis is usually favorable, and there are usually no residual affects.

BODER, Los Angeles.

SCARLATINAL RHEUMATISM AND RHEUMATIC POLYARTHRITIS. LUIGI CARTAGENOVA, Policlinico inf. **15**:369 (Aug.) 1947.

After having synthetically reported the problem of the relation between scarlatinal rheumatism and acute rheumatic polyarthritis, on the basis of the results in previously observed cases, Cartagenova asserts that the precocious form of the disease is due to the scarlet fever virus and the late form to the rheumatic polyarthritis. He confirms, further, the importance of the clinical differential diagnosis and the remarkable help obtained by the red cell sedimentation rate.

FROM THE AUTHOR'S SUMMARY.

ENCEPHALOPATHY WITH EXIT IN SPASTIC HEMIPLEGIA OCCURRING IN THE PRODROMAL PERIOD OF PERTUSSIS. MARY CRISALLI, Policlinico inf. **15**:375 (Aug.) 1947.

The author reports a case of encephalopathy in an 8 year old boy during the prodromal period of whooping cough which ended in spastic paralysis. The author believes these symptoms can be referred to hemorrhage favored by a preceding toxic lesion of the vascular coats.

FROM THE AUTHOR'S SUMMARY.

DO THE SULFONAMIDES HAVE AN INFLUENCE ON THE HEMOGRAM IN SCARLET FEVER AND DO THE SULFONAMIDES PRESERVE THEIR SENSITIZING ACTION DURING SCARLET FEVER? H. BRIEGER, Arch. f. Kinderh. **133**:41 (Jan.) 1947.

When a sulfonamide (sulfapyridine) was given from the first day of the appearance of the scarlet fever eruption, definite changes in the white blood cell picture were observed. The total white blood cell count dropped much faster, and normal values were obtained as early as the ninth day after the onset of the disease. The drop in the total number of white blood cells is caused by a decrease in the number of granulocytes and lymphocytes. The absolute number of segmented white blood cells dropped most rapidly. The number of eosinophils dropped slowly until the fifth day after the onset of the eruption; from the fifth to the tenth day a definite rise of eosinophils was observed. This rise in the number of eosinophils after sulfonamide therapy is explained as a sign of sensitization (beginning allergy) to sulfonamide.

The hemogram during the exanthematous stage of scarlet fever treated with sulfonamide is definitely different from the hemogram during a drug eruption from sulfonamides.

Previous sensitization of the organism to sulfonamide does not give a protection against a simultaneous infection with scarlet fever. Similarly, German measles (rubella), mumps (parotitis epidemica) or chickenpox (varicella) may appear during the period of sensitization to sulfonamide.

ARON, Chicago.

THE RELATION OF THE TYPES OF C. DIPHTHERIAE TO THE CLINICAL PICTURE OF THE DISEASE. S. CHAROCOPOS and J. MARGARITIS, Arch. Greek Paediat. Soc. **1**:25 (April) 1947.

Charocopos and Margaritis studied the types of Corynebacterium diphtheriae (Anderson and co-workers' classification) isolated from 418 children with diphtheria and 42 healthy carriers. They correlated the three types (gravis, intermediate and mitis) to sex, age and seasons of the year, to the localization and form of the disease and to the complications and outcome. From their study they reached the following conclusions:

1. They advise great caution in the acceptance of any relation between the type of the C. diphtheriae and the clinical course and outcome of the disease. 2. The problem of malignant

diphtheria is not solved by the recognition of the gravis type, and the importance of other factors should not be underestimated. 3. Because of the great differences in the results of various workers on this subject, the value of the classification of Anderson and associates should be assessed only after further study of a great number of cases of various epidemics. 4. In view of the lack of constant and indisputable correlation between the three types of C. diphtheriae and the severity of the illness, the hope that the therapeutic means could be further specified has not been realized.

DOXIADIS, Newcastle, England.

INTUBATION AND TRACHEOTOMY IN THE TREATMENT OF LARYNGEAL DIPHTHERIA. S. CHAROCOPOS and M. KOLOKOURI, Arch. Greek paediat. Soc. **1**:72, 1947.

Charocopos and Kolokouri report a study of 1,137 cases of laryngeal diphtheria treated in the Children's Hospital (Athens) during the years 1922 to 1942.

After describing the pathogenesis, the clinical forms and the factors influencing the incidence, Charocopos and Kolokouri present in detail the methods of treatment used by them and by other workers and their results. They describe the advantages, the indications and the complications of intubation and tracheotomy.

The following is a summary of their results. 1. The highest seasonal incidence of laryngeal diphtheria was noticed in November (203 cases), December (197 cases) and October (167 cases), and the lowest, in July (25 cases) and June and August (33 cases in each). 2. The highest age incidence was noticed in the second (300 cases) and the third (244 cases) years of life. 3. There were 313 deaths, or a mortality of 27.4 per cent. The cause of death was myocarditis in 44.4 per cent, myocarditis and bronchopneumonia in 20 per cent, pneumonia in 11.1 per cent and occlusion of the trachea in 6.6 per cent. 4. The percentages for mortality were in the cases in which neither intubation nor tracheotomy was performed, 12.8; in the cases with intubation, 35.5; in the cases with intubation followed by tracheotomy, 40, and in the cases with tracheotomy without preceding intubation, 50.

The treatment indicated in laryngeal diphtheria consists in administration of diphtheria serum as early as possible. If in spite of serotherapy the signs of dyspnea persist and become more marked so that the life of the child is in danger, intubation should be performed, and if this fails to relieve the dyspnea, then tracheotomy should be performed.

DOXIADIS, Newcastle, England.

Acute Infectious Diseases

RARE DYSENTERY SYNDROME. G. TACCONE, Ann. ital. di pediat. **3**:22 (Feb.) 1950.

Taccone reports cases of two little girls who presented diarrhea phenomena during whooping cough. He discusses its pathogenesis.

FROM THE AUTHOR'S SUMMARY.

CEREBRAL RHEUMATISM IN CHILDHOOD. ANGIOLA CANUBI, Ann. ital. di pediat. **3**:63 (Feb.) 1950.

Canubi reports three cases of cerebral rheumatism in children respectively 4, 5 and 7 years old, in whom nervous phenomena have been respectively preceded, accompanied and followed the febrile and articular phenomena. All three children recovered.

FROM THE AUTHOR'S SUMMARY.

THE RESPIRATORY MANIFESTATIONS OF ACUTE ARTICULAR RHEUMATISM. MARIA CHIERICHETTI, Ann. ital. di pediat. **3**:164 (April) 1950.

Chierichetti reports 24 pleuropulmonary manifestations observed among 344 patients with Bouillaud's disease during the years 1939 to 1949 in the Children's Hospital of Milan.

FROM THE AUTHOR'S SUMMARY.

AUREOMYCIN IN THE TREATMENT OF INFECTIOUS MONONUCLEOSIS. GIORGIO BARTOLOZZI, Div. clin. pediat. **48**:169 (March) 1950.

A case of infectious mononucleosis in a child who responded favorably to aureomycin treatment is presented.

FROM THE AUTHOR'S SUMMARY.

PATHOLOGICAL MORPHOLOGY OF RHEUMATIC DISEASE. N. ORLANDI, Lattante **21**:129 (March) 1950.

Photomicrographs illustrate a review of the pathological changes seen in the various tissues of the body in the course of rheumatic fever.

HIGGINS, Boston.

HUMAN TOXOPLASMOSIS. G. DE TONI, Rev. españ. pediat. **5**:317 (May-June) 1949.

The author reviews the literature on the subject. On account of difficulties of communication during the war, Europe was more or less isolated from the work on this disease in the New World. The first case was described in Switzerland in 1946. The first Italian contribution to the subject was not made till June 1948. The author presents a case in a child of 9 years with left-sided jacksonian convulsive attacks. Nothing new is added to the subject by this article.

MILLER, Newark, Ohio.

Chronic Infectious Diseases

INFANTILE TOXOPLASMOSIS: REPORT OF A CASE WITH AUTOPSY. M. B. RODNEY, N. MITCHELL, B. REDNER and R. TURIN, Pediatrics **5**:649 (April) 1950.

A fatal case of infantile toxoplasmosis with autopsy findings is described, bringing to 21 the number of acceptable cases studied at autopsy. The characteristic necrosis of the central nervous system, calcification and hydrocephalus were present in this patient. In addition, focal chorioretinitis and involvement of the spinal cord and of the periorbital and paravertebral striated muscles and the heart were present. Of great interest is the finding of testicular involvement, which has been described in only one other previous case.

FROM THE AUTHORS' SUMMARY.

MENINGEAL REACTIONS AS A DISCREET MANIFESTATION, OR AN INITIAL FORM OF TUBERCULOUS MENINGITIS. ROBERT DEBRÉ, HENRI E. BRISSAUD, PIERRE MOZZICONACCI and BERNARD RENAUX, Ann. pædiat. **174**:337 (June) 1950.

The authors studied the cases of 23 children with slight meningeal reactions which occurred either at the moment of the tuberculous invasions or during the miliary dissemination. These reactions are characterized by either the complete absence or the particular slightness of clinical signs and symptoms. Generally they are only detected by systematic lumbar punctures. They manifest themselves by a very slight cytoalbuminous reaction or by the isolated presence of tubercle bacilli, disclosed only by culture. The disappearance of these reactions is generally speedy, sometimes spontaneous, and sometimes, no doubt, accelerated by streptomycin treatment. They may, however, precede a more serious and even fatal development. At this stage it is impossible to predict the final outcome of the illness.

Streptomycin treatment is indicated in every case, and intralumbar injections should not be discontinued until both clinical and humoral tests leave no doubt that a cure has been achieved. The authors again draw attention to their observations of curable tuberculous meningitis, of serous tuberculous meningitis (Lincoln), of allergic tuberculous meningitis (Móritz) and of tuberculous meningitis with normal cerebrospinal fluid (Léchelle) and come to the conclusion that in every case these are manifestations of an initial phase of tuberculous meningitis that without streptomycin therapy would more frequently proceed toward a fatal issue than toward spontaneous cure.

FROM THE AUTHORS' SUMMARY.

TUBERCULOUS MENINGITIS IN THE LIGHT OF RECENT CLINICAL OBSERVATIONS AND LABORATORY FINDINGS. K. B. CHOREMIS, V. CONSTANTIDINES, S. PANTAZIS, B. KYRIAKIDOS, ATHEN and N. ZERVOS, Helvet. Paediat. acta **5**:5 (March) 1950.

Acute tuberculous adenitis is often accompanied with slight meningism, and occasionally the presence of tubercle bacilli can be demonstrated in the cerebrospinal fluid; the latter finding is of no prognostic value so far as the development of tuberculous meningitis is concerned. Meningism may be severe, and the presence of tubercle bacilli in the cerebrospinal fluid

may result in a strong cellular reaction without producing a typical tuberculous meningitis. The same can be said for miliary tuberculosis; tubercle bacilli may appear in the cerebrospinal fluid without giving rise to meningitis. Patients with tuberculous meningitis that have been passed as clinically cured may still produce a positive culture of Koch's bacillus, although all other laboratory results of studies are negative. Active tuberculosis, especially when bacteremia exists, demands streptomycin therapy. But only in the case of an actual tuberculous meningitis should the streptomycin be given intrathecally—i. e., when there are pathological findings in the cerebrospinal fluid aside from tubercle bacilli.

FROM THE AUTHORS' SUMMARY.

THE EFFECT OF STREPTOMYCIN IN GRAVE FORMS OF OSTEOARTICULAR TUBERCULOSIS IN CHILDREN. A. CABITZA, Ann. ital. di pediat. **2**:350 (Aug.) 1949.

Cabitza studied the alterations of local and general conditions of eight children affected by particularly serious forms of osteoarticular tuberculosis. In each case the conclusions were favorable and agree with the ones drawn from the study of cases with a normal course or a course of moderate severity. He makes some remarks on the duration, dosage, modality and results of the treatment.

FROM THE AUTHOR'S SUMMARY.

HEPATIC RESERVE OF VITAMIN A IN TUBERCULOUS GUINEA PIGS. ALVARO MASI, Riv. di clin. pediat. **48**:25 (Jan.) 1950.

Masi in research on tuberculous guinea pigs found their hepatic supply of vitamin A to be remarkably lessened in comparison with the vitamin A supply noted in healthy guinea pigs.

FROM THE AUTHOR'S SUMMARY.

MENINGOENCEPHALITIS OCCURRING DURING TREATMENT WITH ARSPHENAMINE. A. LANCU and A. NEULANDER, Pædiat. danub. **6**:71 (Aug.) 1949.

In a child 13 years of age suffering from congenital syphilis, grave symptoms of meningoencephalitis appeared after intravenous injection of 0.15 Gm. of neoarsphenamine U. S. P. Teatment for three days with detoxicating and desensitizing substances (sodium thiosulfate, liquid glucose, isotonic sodium chloride solution, calcium gluconate, vitamin C, cardiac drugs, etc.) was unsuccessful. Then penicillin was given for 11 days, a total of 1,000,000 units intramuscularly and 80,000 units intrathecally. The patient made a complete recovery apart from a persisting paresis on the left side of the face.

Specific treatment was started anew, in the beginning with bismuth alone. Arsenic treatment was gradually introduced, administered first by mouth and later parenterally in small doses together with desensitizing drugs. The first dose was followed by a slight reaction which, although the doses already exceeded the one followed by meningoencephalitis, soon disappeared.

Meningoencephalitis is a rare but grave complication of arsphenamine treatment. Its etiology is not clear. The toxic effect of the drug, the size of the doses and the special susceptibility of the patient all may play a role. It is recommended that the sensitivity and constitution of every patient be examined before treatment. Therapy should be started with mercury and bismuth; organic arsenicals should be given only later.

FROM THE AUTHORS' SUMMARY.

BCG IN PARIS. J. H. DE HAAS, Maandschr. v. kindergeneesk. **18**:1, 1950.

During a visit paid in January 1950 to the Pasteur Institute in Paris and the Station Pilote BCG, the following points came to the fore:

1. The vaccine should be carefully prepared, not only in a classic sense (nonvirulence and sterility), but also especially in other ways (culture, emulsion, dry weight, etc.).

2. Freeze-dried BCG is still insufficiently known. It can be supplied in unlimited quantities and keeps well for a year or more. It could enable the cheap use of standard vaccine in several countries.

3. In general, the intradermal method is preferred to the scarification method, especially in mass vaccination.

4. Intradermal vaccination is being carried out as in the International Tuberculosis Campaign (Copenhagen).

5. The tuberculin reaction—the basis of any BCG campaign—is being studied in Paris on a large scale with old tuberculin, purified tuberculin, purified protein derivative and tuberculin ointment.

6. As in the International Tuberculosis Campaign, the Mantoux test with 10 units is used as the strongest reaction before vaccination.

7. The allergic reaction with liquid BCG (bacillary allergy?) is more sensitive than the most sensitive tuberculin reaction. Tuberculin from the BCG strain has not yet been prepared in Paris.

8. Liquid BCG when used as tuberculin brings to light latent allergy, among others in cases of orally vaccinated infants and of old people.

9. The Pilote Station conducts and registers the BCG campaign in Paris. It is developing rapidly into a center of BCG research and BCG instruction.

10. A careful technic is preferred to a quick expansion in order not to endanger again the popularity of BCG.

11. Experience in revaccination is still limited.

12. The BCG campaign in Morocco is being led and fed from Paris.

FROM THE AUTHOR'S SUMMARY.

Diseases of Lungs, Pleura and Mediastinum

SHORT WAVE DIATHERMY AS A THERAPY OF PNEUMONIA IN CHILDHOOD. E. POLÁCEK, Pediat. listy **4**:27, 1949.

Short wave diathermy was of use in interstitial pneumonias, mainly in whooping cough, together with penicillin, sometimes with sulfonamides, or, in less severe cases, by itself. The author and his co-workers use short wave diathermy in cases of pneumonias which do not react to penicillin and sulfonamides and find it a valuable form of treatment.

FROM THE AUTHOR'S SUMMARY.

RECURRING BRONCHITIS AND DENTAL CARIES. G. M. H. VEENEKLAAS and H. J. VAN MAANEN, Maandschr. v. kindergeneesk. **17**:74, 1949.

The authors describe a patient 4½ years old with recurring bronchitis and dental caries of the occlusal surface of the last teeth. Cultures of the carious contents detected among the various pathogenic micro-organisms hemolytic streptococci, to a vaccine of which the patient was hypersensitive. The carious teeth were abrased to the bottom of the cavities. The patient was treated by subcutaneous injections of the hemolytic streptococci vaccine. In the following year his general condition improved considerably. Bronchitis did not occur any more, although influenza occurred in the family and the patient himself contracted common colds with average frequency.

FROM THE AUTHORS' SUMMARY.

TERATOMA BENIGNUM MEDIASTINALE. D. VERVAT, Maandschr. v. kindergeneesk. **17**:116, 1949.

The author describes a case of teratoma benignum in a child 8 months old in which operation was successful.

FROM THE AUTHOR'S SUMMARY.

NEUROLOGICAL COMPLICATIONS IN PRIMARY ATYPICAL VIRUS PNEUMONIA. D. P. R. KEIZER, Maandschr. v. kindergeneesk. **17**:126, 1949.

In 85 cases of primary atypical virus pneumonia there were four cases with neurological complications, which were meningitis, encephalopathy and cerebellar ataxia.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

INFANTILE GASTROENTERITIS AND COLON BACILLICIDE "CATALYTIN." ALEXANDER KOMIS, Arch. Pediat. Clin. **3**:63, 1949.

The author reviews research done since 1886 on the synergy and antagonism of microbes and on antibiosis. The object of this research was to devise a treatment for gastroenteritis by useful microbes. Dr. Komis points out the discovery, in the late nineteenth century, of the colon bacillus as a major counteractive agent in treating gastroenteritis.

As a result of his own research, he has found that his colon bacillicide "catalytin" is curative in various forms of infantile gastroenteritis, ranging from simple enteritis to cholera infantum. He claims that two to six injections of "catalytin" are sufficient to cure intestinal diseases, including bacillary and parasitary dysenteries. The normal function of the colon bacillus is to interact with other intestinal organisms, thus preventing, as well as curing, intestinal disease.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

THE CONTENT OF ALBUMIN AND CELL COUNT OF THE CEREBROSPINAL FLUID IN VIRUS DISEASES OF THE CENTRAL NERVOUS SYSTEM. L. BARTA and Z. ERDÖS, Ann. pædiat. **173**:163 (Sept.) 1949.

This is a report on virus meningitis cases which have been grouped according to the clinical picture into three groups. In group 1 there was an albuminocytological dissociation during the whole course of the illness. In group 2 the proportion between albumin and number of cells was normal to begin with and the dissociation appeared later, while in group 3 pleocytosis and cytoalbuminous dissociation were found.

The authors assume that since the distribution of the cases had an epidemic character and since the cases belonging to group 1 were sharply defined from the others, the cases belonged either to the epidemic or to the sporadic groups which were caused by different types of virus.

FROM THE AUTHORS' SUMMARY.

RESULTS OF BRAIN SURGERY IN CHILDREN. OKONEK, Monatsschr. f. Kinderh. **97**:141, 1949.

Evaluation of operative results in 111 children with intracranial tumors showed medulloblastomas of the cerebellum to be the most malignant neoplasms, with a usual postoperative survival of 15 months. The most benign brain tumors of childhood are the astrocytomas, which occurred as frequently as medulloblastomas but were often difficult to differentiate from each other preoperatively. Radical extirpation of astrocytomas was usually followed by permanent cure. Most tumors of the fourth ventricle, gliomas of the pons and medulla, pinealomas, tumors of the corpora quadrigemina, ependymomas of the third ventricle and supratentorial gliomas were found to be inoperable. Colloidal cysts of the third ventricle near the foramen of Monro are infrequent in children but have excellent postoperative prognoses.

Craniopharyngiomas were found to be operable if in favorable locations. Radical extirpation was in some cases followed by Simmond's cachexia or hyperthermia. The author's survey showed 25 to 30 per cent permanent cures after operation on intracranial tumors in childhood.

HARTENSTEIN, Chicago.

PSEUDOTETANUS, A FORGOTTEN SYNDROME. E. DEN HARTOG-RICARDO, Maandschr. v. kindergeneesk. **17**:59, 1949.

In 1896 Escherich described a form of tetany occurring in boys, which he called pseudotetanus. It was characterized by tonic contractions of the lower extremities, trunk and face, with trismus and risus sardonicus. The musculature of the upper extremities was hardly involved or completely free. The disturbance passed in a few weeks. Subsequent authors felt that it might be a form of encephalitis.

A 10 year old boy is described, who had had difficulties in chewing, stiff muscles and a peculiar gait. There were trismus, risus sardonicus and a marked hypertonicity of all muscles except those of the arms. Reflexes of the legs were hyperactive; those of the arms, normal.

The electric irritability of the affected muscles was decreased. The spinal fluid was normal as well as the blood calcium. There was no indication of tetanus; there were no real muscular contractions. The disturbance passed without any treatment, and after four weeks nothing abnormal could be found. The author was of opinion that the diagnosis of pseudotetanus should be made.

VAN CREVELD, Amsterdam, Netherlands.

Psychology and Psychiatry

PSYCHOSOMATIC PEDIATRICS. SVEN HEINILD, Acta pædiat. **37**:117, 1949.

A study made in a Copenhagen children's hospital shows that 52 per cent of the patients over 2 years of age were suffering from psychosomatic illnesses rather than from purely organic lesions. The importance of future work in pediatric psychiatry and psychology is discussed.

FROM THE AUTHOR'S SUMMARY.

Diseases of Genitourinary Tract

KIDNEY LYMPHATICS AND KIDNEY FUNCTION. W. FREY, Bull. Schweiz. Akad. d. med. Wissensch. **5**:274 (July) 1949.

A nephrotic syndrome may follow changes in the renal lymphatic flow. The renal lymph contains cholesterol in addition to salts, glucose and urea. Cholesterol may be a product of the cellular activity of the tubules.

FROM THE AUTHOR'S SUMMARY.

UREMIC SYMPTOMS PRODUCED IN DOGS WITH INTRACISTERNAL INJECTIONS OF CEREBROSPINAL FLUID FROM UREMIC PATIENTS. P. DE MUNCK, Schweiz. med. **79**:907 (Sept. 24) 1949.

Cerebrospinal fluid was obtained from patients with acute and chronic uremia, the latter due to a periurethral adenoma with distention of the bladder. The fluid was injected intracisternally in dogs in an amount equal to that removed before injection. Soon symptoms of depression, commonly observed in uremic dogs, appeared. The degree of elevation of urea in the blood of the patients who provided the cerebrospinal fluid does not determine its activity. The fluid from a patient with chronic uremia is more active than that of a patient with acute uremia. Usually the dogs appear normal again after about half an hour. The recovery can be hastened by washing out the cisterna magna with normal cerebrospinal fluid.

AMBERG, Rochester, Minn.

"ENURESIS" OF MANY YEARS' DURATION CAUSED BY OPERATION OF A SUPERNUMERARY URETER. GABRIEL MAYER, Med. Klin. **44**:805 (June 24) 1949.

A girl 12 years of age had suffered since birth from involuntary discharge of urine, together with normal emptying of the bladder. A neurogenic weakness of the sphincter or a psychogenic incontinence had been suggested as the cause. On examination a third ureter was found on the right with an extravesical opening in the vestibulum. A piece of the third ureter 10 cm. long was resected, resulting in the disappearance of all symptoms.

AMBERG, Rochester, Minn.

RENAL RICKETS WITH TETANY. F. A. WILLEMYNS and O. MEULEMANS, Maandschr. v. kindergeneesk. **17**:25, 1949.

A boy 8 years old, who probably had had renal disease at the age of 9 months, appeared to have impaired renal function when hospitalized. This was associated with changes of the bones (broad epiphysial spaces filled with a cloudy mass). The initially normal calcium level fell fairly rapidly to 6 mg. per 100 cc. The serum inorganic phosphorus level increased from 5 to 6.5 mg. per 100 cc. Urinary calcium excretion was low. The diagnosis of renal rickets was made. With a low protein diet the blood urea fell from 2,500 to 1,000 mg. per 100 cc. Twice during the hospital stay the child had an attack of tetany which cleared rapidly after an intramuscular injection of 1 Gm. of calcium gluconate. Afterward, 4.5 Gm. of calcium lactate was given daily by mouth. The authors ascribed the tetany to the lowering of

the calcium content, which was caused by the subsiding of the acidosis. The condition was fairly satisfactory, but the child died suddenly nine months after hospitalization.

Postmortem examination revealed pulmonary tuberculosis. The kidneys were rather large with only scant specific tissue, enlarged pelves and distended ureters. There were no tubercles in the kidneys on microscopic examination. In the ribs there was a narrow proliferating cartilaginous area with subperiosteal fibrous proliferations of the corticalis.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Muscles, Bones, Joints and Lymph Nodes

THE EOSINOPHILIC GRANULOMA OF THE BONES. B. WALTHARD and A. ZUPPINGER, Schweiz. med. Wchnschr. **79**:618 (July 9) 1949.

Osteolytic foci due to eosinophilic granulomas of the bones were observed in eight patients, five of them children less than 10 years old. The oldest patient was 17 years of age. The foci were found in the iliac bones, the tibia and the frontal and occipital bones. Of special interest are two patients, 1 and 6 years of age. They were taken ill with the symptoms of a chronic otitis media or of a mastoiditis. The treatment is discussed.

AMBERG, Rochester, Minn.

PENICILLIN THERAPY OF ACUTE OSTEOMYELITIS IN CHILDHOOD. S. SZÜCS and J. LADANYI, Wien. klin. Wchnschr. **61**:343 (June 3) 1949.

The authors discuss the results in 39 cases of osteomyelitis treated with sulfonamides and in 21 cases of the disease treated with sulfonamides and penicillin. In the first group major surgical treatment became necessary in 10 cases, while in the second it was necessary in none. Of the first group, nine healed completely; of the second, 13.

AMBERG, Rochester, Minn.

HYPEROSTOSIS CORTICALIS INFANTUM. L. VAN GOGH, Maandschr. v. kindergeneesk. **17**:51, 1949.

Painful legs were noted in a boy 12 days old. Clinical examination five weeks later showed a well developed boy with painful swelling of the lower jaw and the lower legs, which was caused by new formation of bone, restricted to the diaphysis. A delicate swelling of the local lymph nodes, perspiration, fever (37.5 to 38.1 C.), an enlarged spleen and normochromic anemia with leukocytosis and elevated sedimentation rate were also noted. Bone marrow aspiration showed a relatively inactive red marrow. In view of the typical clinical findings and the roentgenograms, a diagnosis of hyperostosis corticalis infantum was established. The blood level of vitamin C was lowered, but no effect of the deficiency was noted. The hyperplasia of bone increased markedly during the first month of observation, then the painfulness decreased, the fever subsided and the spleen could not be felt any longer. The physical development was not retarded, although roentgenograms taken after 9 months still showed a considerable thickening of the affected bones. Several biopsies were taken. The periosteum was thickened and showed distinct intercellular edema but no signs of inflammation were noted. The bone consisted of delicate but normal trabeculae and edematous connective tissue. Again, there were no signs of inflammation. In the lymph nodes, however, chronic inflammation with proliferation of swollen endothelial cells was seen.

Van Gogh discusses the differences between hyperostosis corticalis infantum and scurvy, congenital syphilis, tuberculosis traumatic periostitis and Ewing's sarcoma. The clinical findings seem to be caused by an infectious agent, with secondary alteration of calcium metabolism. Notwithstanding an extensive search including investigation of viruses, no such agent could be demonstrated.

VAN CREVELD, Amsterdam, Netherlands.

CHONDRODYSTROPHY CALCIFICANS CONGENITA. CORNELIA DE LANGE and TIELINE JANSSEN, Maandschr. v. kindergeneesk. **17**:67, 1949.

The case history, roentgenograms and microscopic details of several internal organs are given of an infant who died at the age of 2 months. Many congenital anomalies were present. The roentgenograms led to the diagnosis of chondrodystrophia calcificans congenita, a rare disease which must not be identified with the "stippled epiphyses" of older children.

FROM THE AUTHORS' SUMMARY.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Arthur F. Abt, M.D., President

Regular Meeting, Feb. 21, 1950

SYMPOSIUM ON CEREBRAL PALSY

Prevalence of Convulsions in Cerebral Palsy. MYER A. PERLSTEIN.

This represents a study of 540 cases of cerebral palsy studied clinically and electroencephalographically. The incidence of convulsions in cases of cerebral palsy with involvement of the pyramidal tract was found to be as high as 50 per cent, whereas in those cases of extrapyramidal involvement only, it was in the neighborhood of 15 per cent. There is a correlation between educability and convulsions in children with brain damage. The value of electroencephalography as a laboratory test in differentiating pyramidal and extrapyramidal lesions is discussed, as well as its use in determining certain therapeutic procedures.

Orthopedic Aspects of Cerebral Palsy. FREMONT A. CHANDLER (by invitation).

Treatment of Cerebral Palsy in an Institution. GERDA B. IRVING.

This discussion of institutional treatment of children with cerebral palsy is based on the experience of my colleagues and me at the Illinois Children's Hospital-School. This is a state institution under the Department of Public Welfare that provides care for 92 children. The children range in age from 3 to 21 years. All children receive residential medical care, physical rehabilitation and schooling. Under the law that established the institution the children must be educable but so severely handicapped that they cannot attend even the public schools for the crippled.

The children present a wide variety of orthopedic and neurological handicaps. At present the population includes 37 children, or 42 per cent, with cerebral palsy. Two of these children are also blind, two are deaf and several others have hearing and visual defects of varying degrees. Of the total group of 37, only 13 are ambulatory. Most of these require braces and crutches or a walker. Treatment as well as schooling of children as severely handicapped as those in our group is of necessity very complex. As an example of the variety of the problems to be met, I will now outline the program that was developed for rehabilitation and education at the Hospital-School.

A number of pediatric and nursing problems are encountered in the general care of these children. On admission the children frequently have signs of malnutrition and vitamin deficiencies. These are due to the difficulty the children have with voluntary opening and closing of the mouth and chewing and swallowing of food. Many children require an hour or more for one meal, and many have to be completely fed. The speech therapist helps materially in overcoming such difficulties as reversed tongue and swallowing motions and improving lip control. With a high calory, high vitamin diet, with the food adequately prepared and chopped if necessary, most of such dietary deficiencies can be gradually overcome.

A large number of children are constipated when first admitted. This may be due to insufficient bulk in the diet or inadequate fluid intake; it may be part of the general spastic condition; it may be secondary to habitual use of laxatives, suppositories or enemas at home, or it may be on an emotional basis. Toilet training is frequently delayed by the inability of the child to talk and make his wants known.

The children's resistance to infections is definitely low, and recurrent respiratory tract infections with chronic sinusitis and otitis necessitate frequent interruptions of the program. Part of the problem is associated with the mechanical difficulties of expectorating and blowing the nose and with the problem caused by aspiration and regurgitation of liquids. For example, about half a

dozen children require daily nasal suction. We have been very satisfied with the results of sulfonamide prophylaxis during the winter months in selected cases.

Dental caries is practically always present and often extreme, since prophylaxis and treatment are difficult to perform in children with cerebral palsy. It takes a specially trained dentist to work successfully with these children. Fluoride prophylaxis frequently cannot be used because of excessive salivation.

Control of epileptic seizures presents the same problems as in general practice.

A variety of drugs such as neostigmine (prostigmine®), trimethadione (tridione®), mephenesin (tolserol®) and members of the nightshade family are being used to enhance relaxation. Evaluation of the effectiveness of these drugs is difficult because spontaneous improvement and relapses occur even without their use. We find that a small number of children definitely respond favorably to drug therapy.

In outlining a program of rehabilitation for each child, we seek the help of medical consultants in various specialties. Good results in treatment can be obtained only by teamwork of various specialists who understand the problem of cerebral palsy. The pediatrician, neurologist, orthopedic surgeon, ophthalmologist, otologist and psychiatrist all have a place in this work. Dr. Chandler has outlined the indications for surgery. Braces are used extensively in the treatment of cerebral palsy. In the spastic child braces are useful in stretching spastic muscles, preventing deformity and protecting weak muscles. For the athetoid patient bracing helps to diminish involuntary extraneous movements and thus aids in the training of controlled purposeful movements. It may be interesting to note that 50 to 75 per cent of cerebral palsy patients have eye symptoms. These usually manifest themselves in eye muscle weakness and imbalance and frequently lead to visual defects. In cases of strabismus, prescription of glasses with incorporation of prisms and use of atropine eye drops often result in marked improvement and facilitate reading. Otological examination and audiometric testing are used to determine degree and type of hearing loss, which if severe may interfere with speech development. Two of our patients received hearing aids, and as a result there was marked improvement of speech under proper training. One of these children appeared very negativistic and uncooperative until it was found that these symptoms were pseudoemotional and were caused by a severe auditory defect. However, true emotional disturbances are frequently found in children with cerebral palsy which may be attributable to the organic brain lesion or may be caused by the child's psychological reactions to his handicap or by environmental factors, such as parental overprotection or rejection. A program of psychotherapy is developed in consultation with a child psychiatrist and is usually carried out by a psychologist or trained social worker.

When the immediate and long term treatment program has been outlined, the physical rehabilitation program gets under way, and the child is enrolled in physical, occupational and speech therapy according to his needs. Specific exercises and activities are prescribed for each youngster, and the program is expanded after periodic reexaminations according to the child's progress. Early workers in cerebral palsy have developed some principles for physical therapy. These include relaxation, muscle coordination, balance, strengthening of weak muscles and stretching of spastic muscles. In promoting reciprocation specially designed tricycles and skiis are used. Various types of walkers are employed for children who cannot use crutches. In occupational therapy improvement of arm and hand function is stressed and special implements to facilitate activities such as eating and writing are constructed. Occasionally wrist splints are used to improve hand function. The different types of cerebral palsy require varying approaches too lengthy for this discussion. The degree of improvement varies, of course, with the severity of involvement, and in all cases much arduous work on the part of the therapist and the patient is involved in producing results.

Like the treatment program, the school program must be individualized to answer the needs of the various handicaps. A different approach must be used for the child who cannot write, talk, hear or see and the one who has a combination of these defects. Special teaching methods and materials have been devised for these children, such as audiovisual aids for the severely motor handicapped, flash cards and word boards for the speech handicapped and still other methods for the blind and deaf. The child with cerebral palsy is more distractable and has a shorter attention span than the average child, and therefore many children require individual tutoring. Diagnosis and treatment of aphasia require special skills, and in this area we are fortunate to receive help from an outstanding neurologist and psychologist.

The school program is supplemented by a vocational program. Here, again, much ingenuity is required to prepare the handicapped person realistically for the future and for a vocation which he can handle both physically and emotionally.

A word about estimation of intelligence in the severely handicapped child with cerebral palsy. Generally speaking, these children are frequently underrated and pronounced defective because motor, language and social adaptive development are delayed in consequence of their illness. Psychological testing is difficult because the standard tests cannot be applied without modifications, and sometimes not at all. To date no satisfactory tests have been devised for general use in cerebral palsy, and even a psychologist experienced in the field is frequently unable to arrive at an estimate of the child's intelligence. In these instances observation of the child's progress in a residential program, as outlined above, rather than routine testing will provide the clues to the child's intellectual capacity.

In conclusion, I would like to stress several points. A program such as is conducted at the Illinois Children's Hospital-School is geared to the needs of the most severely handicapped children. It is not suggested that residential care with such a variety of services is needed or even desirable for all children with cerebral palsy. In the milder cases the patients should remain at home and receive education and treatment in their communities. However, the needs of the group to which I refer are so varied and so great that a long term rehabilitation program which offers intensive treatment and the services of specially trained personnel is necessary for improvement. In addition, these children require so much physical care that the mother is frequently unable to provide it or does so at the expense of her other family responsibilities. If the child is kept at home, he is deprived of opportunities for learning, treatment and social maturation. In such cases the parents often receive no guidance for their own problems, and social maladjustment of the child as well as difficult family situations ensue. By placing their child in a residential school, the parents frequently assume a more objective attitude, and the social workers can help them to understand their child's total needs.

Let me briefly mention that besides serving the handicapped child directly a hospital-school should serve two more objectives—training of personnel and research. The demand for professional personnel with experience in the field of rehabilitation and special education far exceeds the present supply, and workers in many professions are needed to fill the gap. In the field of rehabilitation and especially in cerebral palsy we have to learn a great deal, and there is a wide field for research. An institution with ample material for study and the advantage of long term residential supervision should prove very tempting for the researcher in many areas.

Arthur F. Abt, M.D., *President*

Regular Meeting, March 21, 1950

Gastrointestinal Allergy in Infancy. Arthur H. Rosenblum and Philip Rosenblum.

The allergic basis for certain common gastrointestinal disorders in infants has long been recognized by pediatricians and allergists. A historical review was given indicating the recognition of certain types of diarrhea, colic and vomiting as being on an allergic basis. In this study, the cytology of the stool smear has been correlated with the clinical symptomatology in all cases of suspected gastrointestinal allergy, in cases of other gastrointestinal conditions and also in cases of normal infants and children. A remarkably close correlation between the presence of a decided stool eosinophilia and clinical evidence of allergy was observed in 59 cases. It was also observed that in 76 cases of nonallergic children no stool eosinophilia was demonstrated.

A simple technic of rapid stool examination, using the May-Grünwald stain, was described and slides exhibited. It was observed that the finding of eosinophils in clumps gave presumptive evidence of an allergic gastrointestinal disturbance.

The chief symptoms were found to be diarrhea, colic and vomiting, either in pure form or in various combinations. In all these conditions an excess amount of mucus in the stool was one of the outstanding features. Patients with diarrhea occasionally exhibited the celiac syndrome. Allergic diarrheas were very resistant to the ordinary methods of therapy for diarrhea but responded promptly to removal of the offending food, which was generally cow's milk.

A number of patients with pyloric stenosis were found to show evidences of allergy. However, most patients with allergic vomiting did not have pyloric stenosis and responded to specific treatment. These patients showed a high incidence of other allergic manifestations. These included family histories positive for allergy, eczema, asthma and croup.

Treatment consisted in removing the offending food, which was generally not difficult, as most of the patients were young infants. When cow's milk was removed, substitutes included goat's milk, nutramigen® (carbohydrate and amino acid mixture), mull-soy® (a soy bean preparation) and, in some cases, superheated evaporated cow's milk and goat's milk. Wheat and eggs were common offenders and were often eliminated. Blood counts and skin tests were generally found to be of little value.

Several typical case histories were given.

Diagnosis of Tricuspid Atresia or Stenosis in Infants. BENJAMIN M. GASUL (inaugural thesis).

Neurologic Complications of Herpes Zoster. ADOLPH R. NACHMAN (inaugural thesis).

Treatment of Typhoid in Children with Chloramphenicol (Chloromycetin®). LAWRENCE BRESLOW (inaugural thesis).

Seven cases of typhoid were seen at the Sarah Morris Children's Hospital during 1949. The patients were all Negro children under 6 years of age residing in a congested area on the south side of Chicago. The diagnosis was established by clinical findings, blood and stool cultures positive for Eberthella typhosa and significant titers in serum agglutination tests with typhoid H and O antigens. Four children were seriously ill, two had only moderately severe illness and one had a very mild illness.

In vitro test for sensitivity to chloramphenicol, streptomycin, aureomycin and the sulfonamides were done on the isolated strains of E. typhosa. Although five strains showed a relatively high sensitivity to the sulfonamides, clinical administration of these drugs was of no benefit. Two of four strains were sensitive to aureomycin, but this drug was not used clinically. Sensitivity to streptomycin ranged from 5 to 40 micrograms per cubic centimeter, but no clinical trials were attempted. All strains were sensitive to chloramphenicol—two to 2 micrograms per cubic centimeter, one to 3 micrograms and four to 4 micrograms.

Chloramphenicol was given orally to all patients between the eighth and the twenty-fifth day of illness (average, fifteenth day). The original dose varied between 0.971 and 0.187 Gm. per kilogram a day. This dosage was continued until the child was convalescent, at which time the amount was usually reduced. The duration of therapy was 9 to 18 days, with an average of 15 days. The average duration of fever after the start of therapy was 3.5 days. Two blood cultures remained positive for E. typhosa for more than three days after treatment was begun. Stool cultures became negative for the bacilli after an average of six days.

All patients made a complete recovery. One case was complicated by pneumonia. There were no recurrences or drug reactions except nausea. Several patients showed a pronounced leukopenia that rapidly returned to normal after cessation of therapy.

Arthur F. Abt, M.D., *President*

Regular Meeting, April 18, 1950

RESIDENTS' COMPETITION PROGRAM

Effect of Streptomycin on the Pathological Lesions of Miliary Tuberculosis and Tuberculous Meningitis in Infants and Children. HERBERT HERZON (from the Children's Division, Department of Pathology and Department of Neuropathology, and the Hektoen Institute for Medical Research, Cook County Hospital).

The effects of streptomycin on the pathological lesions in 26 cases (23 infants and children, 3 adults) of combined miliary tuberculosis and tuberculous meningitis were reported. After prolonged therapy (a minimum of 60 to 90 days) far advanced healing changes were found in the miliary lesions and in the exudate of the meninges. Notwithstanding, there were

usually present caseous or incompletely healed miliary foci and similarly unhealed foci in the meninges. The pathodynamics of healing of tuberculous lesions in the meninges and viscera under the influence of streptomycin features a process of diminishing cellularity and progressive fibroplasia. Healing was prominently displayed in the miliary lesions after prolonged therapy and was by fibrosis and eventual hyalinization. Healing, however, was dependent on the size of the miliary lesion, and caseation persisted in lesions greater than 400 to 600 microns. In two cases the presence of the primary tuberculous focus was not detected and it was presumed that this focus had healed without leaving demonstrable evidence of its former presence.

In spite of prolonged streptomycin therapy, caseous foci, such as in the primary pulmonary lesion and in the pulmonary lymph nodes, persisted in the majority of cases. These foci are presumed to be the sites of origin of repeated hematogenous disseminations of tubercle bacilli. The healing tendency in the exudate in the meninges was not so dramatic as that in the miliary lesions in the viscera. While healing of various degrees was present, usually proportional to the duration of life and therapy, there were also found large or minute areas of unadulterated fresh caseous exudate in 23 of 25 brains studied. Frequent features of the brain in streptomycin-treated cases were: (1) necrotic or ischemic softenings in the basal ganglions on the side opposite the hemiparesis noted in life (31 per cent of cases), (2) greater incidence of marked degrees of communicating internal hydrocephalus than had formerly been observed in untreated cases and (3) selective involvement of the stem of the sylvian fissure with a thick granulomatous necrotic exudate, within which occurs necrotizing endarteritis of branches of the middle cerebral artery supplying the basal ganglions, the cause of the ischemic softenings in the rostral basal ganglions. Relapse in streptomycin-treated tuberculous meningitis was explained as resulting from either a repeated fatal miliary dissemination to the meninges from unhealed caseous foci in the body or local breakdown of minute caseous foci in the meninges. The former explanation appears more plausible for the majority of cases. Definite healing of meningeal exudate can be effected without resort to intrathecal therapy, the major share of healing apparently resulting from the streptomycin reaching the exudate by way of the meningeal capillaries rather than the streptomycin in the cerebrospinal fluid.

Preoperative and Postoperative Growth Patterns in Congenital Heart Disease as Shown by Wetzel Grid. MARY E. RICHARDS (from the Children's Memorial Hospital).

The purpose of this study was to ascertain the characteristic growth patterns of children with congenital heart disease and to determine the effect of operation on these patterns.

A brief review of the literature pertaining to growth in congenital heart disease was presented.

Sixteen patients on whom height and weight records were available and who were operated on for congenital heart disease at Children's Memorial Hospital were selected for analysis. Nine of these children had patent ductus arteriosus and seven had tetralogy of Fallot. The Wetzel grid was employed as a graphic means of portraying growth.

Although the group of cases was small and the postoperative follow-up period relatively short, certain definite trends were apparent. The children with patent ductus arteriosus uniformly showed significant acceleration of growth after operation, while those with tetralogy of Fallot showed little or no acceleration, or actual decrease in rate of growth after surgery, in spite of clinical improvement in cyanosis and exercise tolerance.

The accepted mechanism of growth retardation in patent ductus arteriosus is the presence of an arteriovenous shunt, while that in cyanotic congenital heart disease is tissue anoxia. Therefore, the results obtained in this series may be due to the fact that operative interruption of the patent ductus arteriosus eliminates the cause of growth retardation, whereas the surgical creation of an artificial ductus in patients with tetralogy of Fallot relieves the anoxemia but substitutes a growth-retarding arteriovenous shunt.

Use of Detergents in the Treatment of Fibrocystic Disease of the Pancreas. NORMAN H. BLATT (from the Children's Memorial Hospital).

This report is concerned with the use of detergents as an aid in the treatment of patients with fibrocystic disease of the pancreas. With detergents, the addition of fat to the diet

resulted in absorption of the fat from the gastrointestinal tract with subsequent weight gain and no disturbance in the number and character of the stools.

In the plan of study, evaporated or homogenized milk was added slowly to the diet in place of skim milk until the patient was taking 30 ounces (850 Gm.) of milk daily. The detergent used in this study was Sorlate (sorethytan [20] monooleate). A total of 6 Gm. of Sorlate in divided doses was given for each 30 ounces of homogenized or evaporated milk taken over a 24 hour period. In addition, the patients were given: (1) a high protein, high carbohydrate diet; (2) a water-soluble vitamin A preparation (50,000 units daily); (3) pancreatin (1 teaspoonful a meal), and (4) sulfonamides, penicillin or aureomycin as needed for upper and lower respiratory tract infections. The management of the control patients was similar except that they received no milk containing fat and no Sorlate.

There were eight patients in the series. Five children received homogenized or evaporated milk with Sorlate and the other three children served as controls.

Four of the five patients in the experimental group had a significant weight gain. Patient 1 gained 3 pounds 14½ ounces (1,770 Gm.) in two months; patient 2 gained 1 pound (450 Gm.) in one month; patient 3 gained 6 pounds 4 ounces (2,830 Gm.) in 5½ weeks. For the first three weeks patient 3 also received aureomycin. Patient 4, an obese child despite the fact that he had fibrocystic disease, gained ¾ pound (340 Gm.) in six weeks. Patient 5 gained 2¼ pounds (1,020 Gm.) in five weeks.

The control patients gained less than a pound each, except the one who took aureomycin for one month. He gained 1 pound during that period.

Criteria for the Diagnosis of Nephritis in Children. MARVIN E. COOPER (from the Children's Division of Cook County Hospital and the Hektoen Institute for Medical Research).

The problem of differentiating type I (acute, postinfectious, hemorrhagic) nephritis from type II (chronic, insidious, nephrotic) nephritis has presented itself many times. Because of the marked difference in prognosis, this study was undertaken by my colleagues and me in an effort to determine some diagnostic measures which would aid in differentiation.

The study was based on examination of the serum antistreptolysin titer response; various serum protein fractions, namely, total protein, "true" albumin and gamma globulin, and the total serum cholesterol values in children with type I and type II nephritis. The data were based on 42 cases of nephritis in children who were hospitalized and followed at the Children's Division of Cook County Hospital.

Type I nephritis is mainly a disease of children and young adults. Clinically, the onset is about 7 to 14 days after an upper respiratory tract infection, with malaise and minimal swelling about the face, eyes and legs and an accompanying hematuria. The serum antistreptolysin titer is elevated above the normal limits, and in our series it averaged 389.6 units. The results of serum protein determinations are all within normal limits, including total protein, "true" albumin and gamma globulin. The figures are 7.5, 3.7 and 1.3 Gm. per 100 cc. respectively. The total serum cholesterol also is within the normal range, the average being 201.8 mg. per 100 cc. The prognosis of type I nephritis is favorable in the vast majority of cases.

Type II nephritis manifests itself clinically as the "nephrotic" syndrome. The edema is the most characteristic finding and is insidious in onset and generally massive in nature. Gross hematuria is usally absent. The serum antistreptolysin titers averaged 41.9 units. The following are the results of serum protein fractionations: total protein, 3.7 Gm. per 100 cc.; "true" albumin, 0.63 Gm. per 100 cc., and gamma globulin, 0.17 Gm. per 100 cc. The total serum cholesterol was markedly elevated, with an average of 668.5 mg. per 100 cc. The only statement which can be made concerning the prognosis in type II nephritis is that it must be guarded.

It is our belief that we are dealing with two separate and distinct disease processes. No conclusions are drawn from these observations about the possible etiologic factor or factors in either type I or type II nephritis. Both types follow specific patterns and courses, with type I offering a more favorable prognosis. In no case has type I nephritis developed into a "nephrotic" syndrome, and none of the cases of type II nephritis in this series gave a history of previous type I nephritis.

Use of Sulphetrone in Combination with Streptomycin in the Treatment of Tuberculosis in Children. M. NIERENBERG (from the Sara Morris Hospital for Children, Michael Reese Hospital).

A group of 11 cases of tuberculosis in children treated with combined Sulphetrone (tetrasodium 4:4'-bis-[gamma-phenyl-N-propylamino]-diphenylsulfone-alpha:gamma:alpha'gamma'-tetrasulfonate) and streptomycin are presented as a preliminary report. The cases represented various forms of tuberculosis in infants and children ranging in age from 6 months to 8 years.

Dihydrostreptomycin was given in doses of 1 Gm. daily in 2 to 4 equally divided doses, and Sulphetrone was given by mouth in gradually increasing doses to obtain and maintain blood levels of 7.5 to 10 mg. per 100 cc.

Three cases are presented in detail, and a chart of the results of the over-all study is given. The patients included two with meningitis, both of whom died; one with miliary pulmonary disease who made a complete recovery, which was attributed to streptomycin; one having pleurisy with effusion who showed no response to either drug but recovered gradually; three having progressive primary tuberculosis with cavity formation who showed gradual improvement which was attributed either to streptomycin or to the host resistance; two having primary tuberculosis with tracheobronchial adenitis (in one of them marked progression of the disease developed despite therapy), and two with cervical adenitis and sinus formation who recovered gradually with no definite effect related to Sulphetrone demonstrable.

Toxic effects attributed to the use of Sulphetrone included an almost universal hemolytic anemia of varying severity and the appearance of unexplained transient cyanosis in two cases.

Summary.—No beneficial effects were demonstrated other than those which could be accounted for on the basis of the streptomycin or the expected course of the untreated disease.

Emphasis is placed on the appearance of severe hemolytic anemia necessitating withdrawal of the drug in several instances despite low blood levels.

Sulphetrone, either alone or in combination with streptomycin, could not be recommended as being efficacious in the treatment of tuberculosis in children.

News and Comment

ANNOUNCEMENTS

Fellowship in Pediatric Neurology.—The pediatric neurology department of the children's division of Cook County Hospital is now accepting applications for a fellowship. For information concerning this appointment, write to Dr. Abraham Levinson, Chief of Staff, Cook County Children's Hospital, Chicago 12.

Pediatric Postgraduate Course.—Harvard Medical School will offer a pediatric postgraduate course at the Burnham Memorial Hospital for Children, Massachusetts General Hospital, Boston, June 11 to June 23, 9:00 a. m. to 4:30 p. m. daily. The course is under the direction of Allen M. Butler, Professor of Pediatrics. Further information concerning these courses may be secured by writing Courses for Graduates, Harvard Medical School, Boston.

Coming Examinations to be Held by the American Board of Pediatrics, Inc.—The American Board of Pediatrics, Inc., will hold oral examinations on March 2, 3 and 4 in New Orleans; on March 30 and 31 and April 1 in Cincinnati, and on May 5, 6 and 7 in Atlantic City, N. J.

CORRECTION

In the article by Dr. Abraham Kaplan on "Ependymoma of Lateral Ventricle," in the December issue, page 964, it was incorrectly stated that Dr. Joseph A. Trackman, New York, was called to treat an elderly woman. Dr. Trackman is a pediatrician. He was called to see one of his patients, a child with an infection of the upper respiratory tract. When his examination of the patient was completed his attention was called to another child, who was visiting in the house at the time. The second child was the subject of Dr. Kaplan's report.

Obituaries

LEONARD PARSONS, M.D.
1879-1950

The passing of Sir Leonard Gregory Parsons, M.D., F.R.S., F.R.C.P., F.R.C.O.G., has removed from British pediatrics a noble and notable figure, a leader of men and of research and a gentleman who never wished harm to anyone and to whom everyone who knew him gave thanks for his kindness, courtesy and unselfish guidance. In his early professional life he had experience in general practice, and later as a general physician he spent many years in gaining his vast experiences with those long term aspects of disease which, in due course, were to intensify his interests in pediatrics. Parsons rightly believed that early recognition of disease in infancy or childhood may prevent serious illness later on; and so, from the teaching point of view, he was able to inculcate wide general principles and extend the horizon of the undergraduate.

Parsons had a worldwide friendship and professional reputation, not least in the United States, where he had the distinction and personal pleasure of giving the Rachford Lecture (1931), and in Canada, where he gave the Blackader Lecture (1946). His American friends were frequently seen at the Children's Hospital, Birmingham, and one looks back to those days of the most cordial visits of Kenneth Blackfan, Graeme Mitchell and others.

In clinical ability Parsons excelled, and his handling of a difficult situation was always an instructive exercise. In research he had unusual capacity for fathering appropriate teams; and, despite busy private practice, he was responsible for wide fields of original research, most significantly in nutritional problems, renal disease and rickets, the celiac syndrome, the anemias of childhood and finally in aspects of antenatal pediatrics. He suggested the generic term hemolytic disease of the newborn and gave a good deal of attention to the clinical aspects of rhesus incompatibility.

His distinction grew, and he was awarded the Moxon Medal (1942) by the Royal College of Physicians, and the obstetricians elected him a fellow of their college and invited him to deliver before them the Blair-Bell Lecture on "Ante-Natal Paediatrics."

In World War I he did foreign service with the R.A.M.C. in Greece; in World War II he was given high responsibilities in the hospital organization in England. Over and above all this, he kept his mind and hands on all else and refused to let anything go. As Dean of the Faculty of Medicine, Birmingham University, he showed uncanny abilities in attracting good heads of departments and so built up a most flourishing school, which will greatly miss his pointed ways of conscientious service and devoted attention to the students' welfare. Publication of "Diseases of Infancy and Childhood" (1933) showed Parson's great strength as a writer and as an editor, and he probably saw an advance copy of his final effort in "Modern

Trends in Paediatrics," just published. His guest editorial in "The 1950 Year Book of Pediatrics" may appropriately lie as a memorial to his Anglo-American reputation, the style being representative of his mature and philosophical judgment in the field of medicine which engaged so much of his life and which has added to the international unity of friendship of pediatricians.

His religious attention daily included a reading from the Bible: His beloved Milton wrote lines appropriate for Leonard Parsons' memorial:

"Lord God of Hosts that reigns on high,
That man is truly blest
Who only on thee doth rely
And in thee only rest."

A. V. N.

Book Reviews

Pollen-Slide Studies. By Grafton T. Brown. With a foreword by Wallace M. Yater. Price, $6. Pp. 135, with 98 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1949.

This beautiful book was written to assist persons, particularly allergists, not trained in botany to study by simple but reasonably accurate methods the qualitative and quantitative pollen and fungous spore content of the air. This is done through the medium of a text which is chiefly explanatory of 182 separate drawings and 34 photomicrographs. The relation of meteorologic factors to pollination is clearly and briefly discussed. In a book of this character the theory of Wodehouse that the onset and offset of ragweed pollination are determined by photochemical reactions should have been mentioned, along with the accepted theory that the offset of pollination is caused by frost acting to kill the short ragweed. There is also a table of nineteen pages listing the pollens seen on the author's slides made in the District of Columbia from 1938 to 1941. This, having little more than local interest, could easily have been omitted. The various types of pollen, fungous spores and smuts are illustrated as they appear on the petrolatum-coated slides used in everyday practice. Eeach type of pollen grain is diagrammed and illustrated by a larger and more detailed drawing and, finally, by a photomicrograph. The technical language used is simple and explicit. For the allergist or technician desiring to do pollen counts with any degree of understanding, this book should prove invaluable.

Advances in Pediatrics. Volume 4. Edited by S. Z. Levine, A. M. Butler, L. E. Holt Jr. and A. A. Weech. Price, $6.50. Pp. 316, with 37 tables and 54 figures. Interscience Publishers, Inc., 215 4th Ave., New York 3, 1949.

As in previous volumes, the selection of articles is excellent, covering subjects of current and permanent interest and written by authors who have established worldwide reputations in their fields. For the first time, contributors from foreign countries were selected, a policy which made it possible to draw from an even greater number of authorities. The choice of subjects, too, has somewhat changed from that for previous volumes, inasmuch as rare conditions, as described in the article by Freudenberg (Basel, Switzerland) on cystinosis and in the one by Siwe (Lund, Sweden) on reticuloendothelioses, are discussed. Although this is a desirable policy from the point of view of the pediatrician, who will be able to get up-to-date information with greatest thoroughness on subjects which otherwise require much searching in the literature with, as in the case of cystinosis, most of it in foreign writings, the general practitioner will rarely want to assume the responsibility of managing such a patient. On the other hand, the remaining articles are of general interest from diagnostic, therapeutic or preventative points of view. They all are characterized by their thoroughness in dealing with the subject and, although they represent, of course, quite ardently the point of view of the author, none of the contributors fails to discuss other views in detail. This applies particularly to such controversial subjects as "Diet in Diabetes in Childhood" by Lichtenstein (Stockholm, Sweden) and "Combined Immunizations" by Lapin (New York). The three other articles, "Treatment of Congenital Syphilis with Penicillin" (Platou, New Orleans), "Erythema Nodosum" (Gross and McIntosh, New York) and "Subdural Hematoma in Infancy" (Ingraham and Matson, Boston), are of a practical nature and timely character for the specialist, as well as for the practitioner attending children.

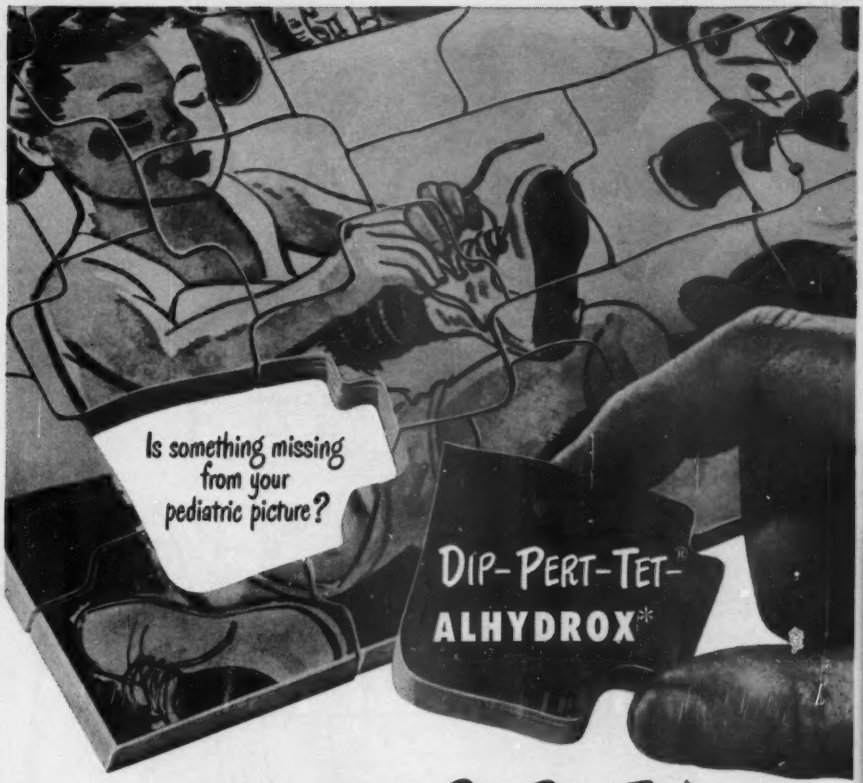
The yearly addition of a new volume of "Advances in Pediatrics" may be considered a must for the pediatrician's library.

Die Bazillenruhr. By Ludwig Roehmheld. Price, 10.80 marks. Pp. 125, with 4 tables and 20 graphs. Georg Thieme Verlag, Diemershaldenstrasse 47, Stuttgart-O (American Zone), 1949.

Dysentery is an epidemic disease and is of particular importance during wartime. Under pathogenesis the author considers climatic, constitutional, hygienic and psychologic factors as forming the basis for the bacterial processes necessary for an epidemic. The clinical course is described in detail and illustrated by many case reports and graphic descriptions of laboratory findings. Diarrhea, sometimes followed by constipation, peritonitis without perforation, general symptoms, circulatory symptoms, fever, water and mineral metabolism, cutaneous and central nervous system symptoms and emotional behavior are discussed. Duration, complications and prognosis are taken up. Little space is allotted to bacteriologic and epidemiologic considerations. Immunization against dysentery is considered of questionable value and of considerable danger, causing occasionally severe attacks of the disease, and, if done after the epidemic has started, it may provoke severe illness. The author's own experience indicates that immunized patients have less severe attacks, but his results are, according to his own admission, statistically not significant.

Only three and a half pages are devoted to pathology, diagnosis and differential diagnosis. Under therapy the author discusses prophylaxis and early therapy, dietary measures and local therapy in the form of medicated enemas. Emphasis is laid on cardiac stimulation and blood transfusions, but regrettably little is said about the actual establishment of water and mineral balance. Medicinal therapy is discussed in more detail. The author states that there is limited value in the early use of cathartics and in the symptomatic relief from administration of spasmolytic drugs; he rejects opium therapy and is of the opinion that sulfonamides have replaced absorbing and astringing medicaments. Various sulfonamides and their beneficial and toxic effects are discussed. The use of polyvalent bacteriophages or serums was of no value; the monovalent phages or serums seemed beneficial, but because they have to be specific to the epidemic they were difficult to obtain and, therefore, technically impractical. Further investigation on these points is considered necessary by the author. The last chapter deals superficially with organizational questions, such as isolation procedures, housing, personnel and records.

The book describes essentially the experiences of the author with dysentery, particularly under wartime conditions, and with its 596, mostly German, references it offers a chance for further reading of the European literature on this subject.



ALHYDROX ADSORBED DIP-PERT-TET†

BUILDS MAXIMUM... DURABLE IMMUNITY

Alhydrox Increases Dip-Pert-Tet Antigenicity—In actual usage as well as reported clinical studies it has been shown that Dip-Pert-Tet Alhydrox produces uniformly superior levels of serum antitoxins. [1, 2, 3]

Alhydrox Reduces Dip-Pert-Tet Reaction Frequency—Prove it to yourself, Doctor . . . vaccinate 25 patients with a plain or alum precipitated combination and another 25 patients with Cutter Dip-Pert-Tet Alhydrox. You will see for yourself that there is a minimum of local reactions with Alhydrox adsorbed Dip-Pert-Tet.

Depend On Dip-Pert-Tet Alhydrox—for simultaneous immunization against Diphtheria, Pertussis, Tetanus. High pertussis count—each cc. contains 30,000 million Phase 1, H. pertussis organisms.

Insist on CUTTER
DIP-PERT-TET ALHYDROX
A FIRST NAME IN COMBINED TOXOIDS

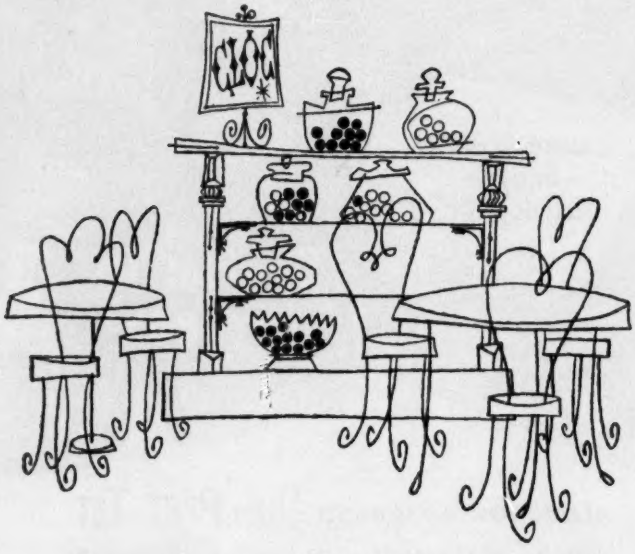
*Cutter Trade Name. †Dip-Pert-Tet Alhydrox—Purified Diphtheria and Tetanus Toxoids and Pertussis Vaccine combined, Aluminum Hydroxide adsorbed.

1. Miller, J. J., Jr., and Ryan, Mary Louise, The Duration of Serologic Immunity, Pediatrics 1:8, Jan., 1948.
2. Lapin, Joseph L., Combined Immunizations, Advances in Pediatrics, Vol. IV, Interscience Publishers, Inc., New York, 1949.
3. Costello, Cyril, Improved Methods in Combatting Tetanus, J. Missouri M. A., 46:582, Aug., 1949.

CUTTER LABORATORIES • BERKELEY, CALIFORNIA

Producers of famous purified Dip-Pert-Tet Plain, a product of choice for immunizing older children and adults.

tastes as good as CANDY



White's **Cod Liver Oil Concentrate tablets**

. . . provide vitamins A and D in easy-to-take tablets. Because of their pleasant flavor, most children prefer to chew them like candy. Yet the tablets are small enough to be easily swallowed, even by young children.

Each White's CLOC Tablet is equivalent in vitamin content* to one teaspoonful of cod liver oil and supplies 312 units of vitamin D, plus 3,120 units of vitamin A. White's Cod Liver Oil Concentrate Tablets are inexpensive and especially suited to maintaining antirachitic protection throughout the years of active growth.

WHITE LABORATORIES, INC.

Pharmaceutical Manufacturers, NEWARK 7, N. J.

*U.S.P. Minimum Standards.

When Lactation Fails

Rx LACTOGEN®

When the supply of breast milk is inadequate or when lactation fails entirely, there is no better formula than Lactogen. Designed to resemble mother's milk, it consists of whole cow's milk modified with milk fat and milk sugar. It differs, however, in one important respect: the protein content of Lactogen in normal dilution is one-third greater than that of mother's milk--2.0% instead of 1.5%.

A Complete Infant Formula In One Package

Lactogen contains all the ingredients of a well-balanced infant formula. In addition, it is fortified with iron to compensate for the deficiency of this mineral in milk.

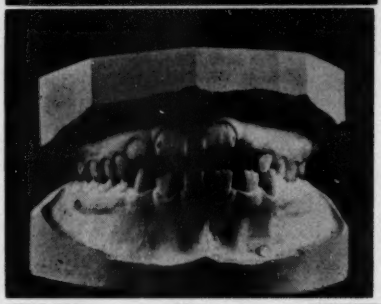
Easily Prepared ... Merely Add Water

Lactogen is simple to use. The prescribed amount is stirred into warm, previously boiled water. Either a single feeding can be prepared, or the entire day's quantity can be made up and stored in the refrigerator until used.

THE NESTLÉ COMPANY, INC.
COLORADO SPRINGS, COLORADO

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

NOTABLY HIGH IN PROTEIN CONTENT
Lactogen contains a generous amount of protein ... more than enough to satisfy every protein need of the rapidly growing infant.



Untoward Results

OF PERSISTENT FINGER-SUCKING

MODEL

is 7½ years old. Unretouched photographs and description from a leading children's dental clinic.

Hand—sucked two middle fingers left hand since age 4. Note deformity caused.

Mouth—case shows deformed shape of mouth and displacement of teeth due to pressure of fingers.

WHEN TREATMENT IS INDICATED . . .
--prescribe THUM TRADE MARK

Contains capsicum 2.34% in a base of acetone nail polish and isopropyl alcohol.

WRITE FOR FREE SAMPLE

NUM SPECIALTY CO. 4614 Fifth Ave. Pittsburgh 13, Pa.

SUPPLEMENT to EXPERIENCE

A.M.A. Archives of INTERNAL MEDICINE

UNDER some circumstances, sometime in his career, practically every physician becomes an internist. Contact with forward-moving practices and opinions in the internal medicine field . . . provided in A. M. A. INTERNAL MEDICINE . . . supplies confirmation and supplements experience for both the specialist and the physician in general practice.

Featured each month will be comprehensive original articles, case reports, clinical studies, progress reports, correspondence, news and comment, book reviews.

Able editorial leadership.

Outstanding contributions.

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois.

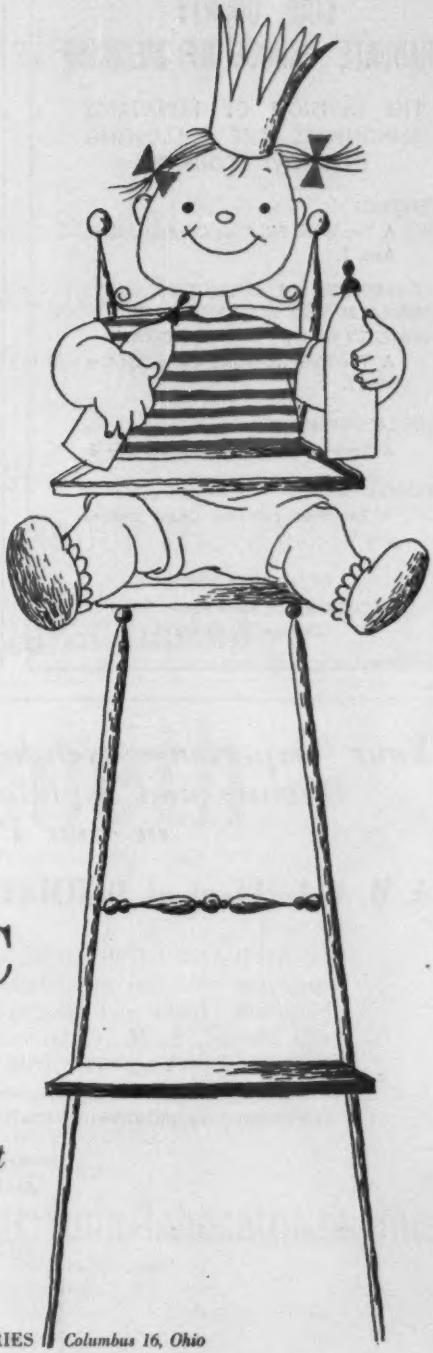
Please Begin My Subscription to A. M. A. Archives of INTERNAL MEDICINE with the Next Issue.

.....M.D.
.....STREET
.....CITY & STATE

$10.00 YEARLY
$11.00 FOREIGN $10.40 CANADIAN

Sitting pretty...

That's the clinical picture shown by the infant started and maintained on SIMILAC from birth to birthday. Zero curd tension, adequate vitamin C supply and 1½ to 1 calcium-phosphorus ratio are but a few of the reasons why...



SIMILAC

is so similar to human breast milk that there is no closer equivalent

SIMILAC DIVISION • M & R LABORATORIES *Columbus 16, Ohio*

COOK COUNTY GRADUATE SCHOOL OF MEDICINE

THE DIVISION OF PEDIATRICS ANNOUNCES THE FOLLOWING INTENSIVE COURSES:

PEDIATRICS
A Two-Week Full-Time Course starting April 2.

THE DIAGNOSIS & TREATMENT OF CONGENITAL AND ACQUIRED HEART DISEASES IN INFANTS AND CHILDREN
A Two-Week Full-Time Course starting May 7.

CLINICAL PEDIATRICS
A Twelve-Month Course starting July 2.

CEREBRAL PALSY
A Two-Week Full-Time Course starting July 9.

For Information Address:
REGISTRAR, 427 South Honore Street, Chicago 12, Illinois

MICHAEL REESE HOSPITAL POSTGRADUATE SCHOOL

RECENT ADVANCES IN PEDIATRICS
Diagnostic and Therapeutic Measures
By
Members of the Department of Pediatrics and Cooperating Departments
Course Supervision by B. M. Kagan, M.D., Chairman, Department of Pediatrics

MAY 21st TO MAY 26th, 1951
(FULL-TIME)

Presentation of Clinical and Didactic Material

Tuition: $50.00

For further information and a detailed program, address:
Dr. Samuel Soskin, Dean
29th Street & Ellis Ave., Chicago 16, Illinois

Your "experience exchange" in the field of Skin Diseases and Syphilis—A valuable guide in your Practice—

A. M. A. Archives of DERMATOLOGY and SYPHILOLOGY

SIGNIFICANT DEVELOPMENTS reported monthly to the specialist and the physician in general practice. From hospitals, clinics and government treatment centers here and abroad, A. M. A. Archives of DERMATOLOGY and SYPHILOLOGY gathers news of current trends in treatment and diagnosis, group case studies, clinical notes and comments on cutaneous conditions and syphilis.

Well illustrated.

Ably edited.

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois.

Please Begin My Subscription to A. M. A. Archives of DERMATOLOGY and SYPHILOLOGY with the Next Issue.

.....M.D.
.....STREET
.....CITY AND STATE

$12.00 YEARLY
$13.50 FOREIGN $12.40 CANADIAN

clinically accepted

for
increased safety
high degree of efficacy
excellent palatability

in triple
sulfonamide therapy

council-accepted

tri-sulfameth

Each 5 cc. (approx. one teaspoonful) of syrup or each tablet provides:

Sulfamethazine	0.165 Gm.	(2.5 gr.)
Sulfadiazine	0.165 Gm.	(2.5 gr.)
Sulfamerazine	0.165 Gm.	(2.5 gr.)
Sodium Citrate*	0.5 Gm.	(7.7 gr.)

*not contained in Tri-Sulfameth Tablets

"Trials of sulfonamide combinations . . . have indicated that the occurrence of crystalluria can be decreased to negligible proportions." Virginia Medical Monthly 75:56, 1949.

PROFESSIONAL SAMPLES ON REQUEST

casimir funk laboratories, inc.
affiliate of U. S. Vitamin Corporation
250 East 43rd St., New York 17, N. Y.

The Case of the Missing Vitamin C

You'll find the oranges in this crate much alike in size and appearance. They're sun ripened and tree ripened . . . highly desirable for adult consumption.

Yet for *controlled pediatric feeding*, the required Vitamin C content of these oranges may be missing – as low as 19 mg/100 cc.

What happened to the "missing Vitamin C"? Laboratory tests prove that nature is inconsistent in supplying ascorbic acid. Oranges from the same grove, even from the same tree vary widely in Vitamin C potency. Time also takes its toll. The Vitamin C content of fresh oranges may be further reduced in shipping and storage.

The Vitamin C *is not missing* in Bib! Through field laboratory control, testing right in the grove, Bib selects only fruit endowed by nature with an abundance of Ascorbic Acid. And to avoid the Vitamin C deterioration which may occur during the time of shipping and storage, Bib maintains a constant flow of fruit from grove to finished pack.

It is the exercise of such exacting controls that made it possible for Bib to maintain *an average of 49.0 mg/100 cc NATURAL ascorbic acid** for its entire 1949/1950 pack. Such controls make it possible for Bib to guarantee that each individual container retains *no less than 40 mg/100 cc NATURAL Ascorbic Acid* when packed.

As added assurance, laboratory analyses of every batch are made by a government official, and, together with corresponding samples, are registered with the AMA's Council on Food and Nutrition.

Experience shows that many babies who could not tolerate other types of orange juice take happily to Bib. Scientifically flavor-controlled, and with troublesome citrus oil reduced to a negligible trace, Bib tastes the same day after day.

For feeding ease, Bib reduces the fruit cells to microscopic size, enabling the juice to flow freely through bottle nipples, eliminating the need for straining – no mixing, nothing to add . . . just open, pour and feed.

Professional full-size samples and literature available on request. Write to The Bib Corporation, P.O. Box 866A, Lakeland, Florida.

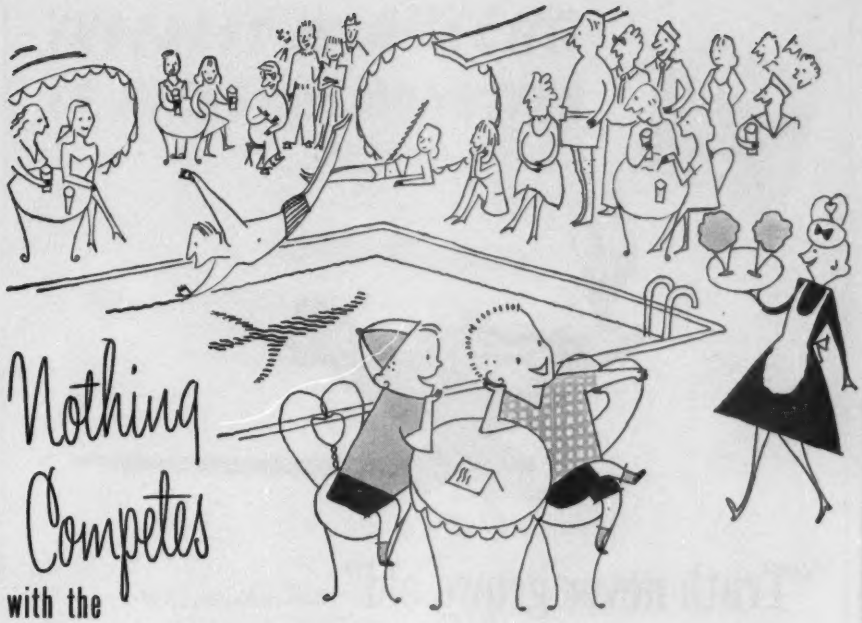
BIB

In 4 ounce, individual feeding, sterilized containers.

DOCTORS PRESCRIBE BIB . . . MOTHERS PREFER BIB . . . BABIES LOVE BIB

**As reported by the Council on Foods & Nutrition in a recent issue of the J.A.M.A.*

THE BIB CORPORATION · LAKELAND, FLORIDA



Nothing Competes with the Lure of Sweets

Tasty Suspension with "Built-in" Alkalinizer

Palatable, orange-flavored DUOZINE Suspension provides, per teaspoonful, 0.15 Gm. each sulfadiazine and sulfamerazine, plus 1.5 Gm. sodium citrate. This liquid is especially good-tasting when diluted in water or fruit juice. In one-pint bottles.

JUNIOR'S in for a pleasant surprise at medicine time when you prescribe attractive, good-tasting DUOZINE *Dulcet* Tablets. Here's a potent sulfonamide combination in orange-colored, candy-like cubes—not a bit like medicine, yet accurately and uniformly medicated.

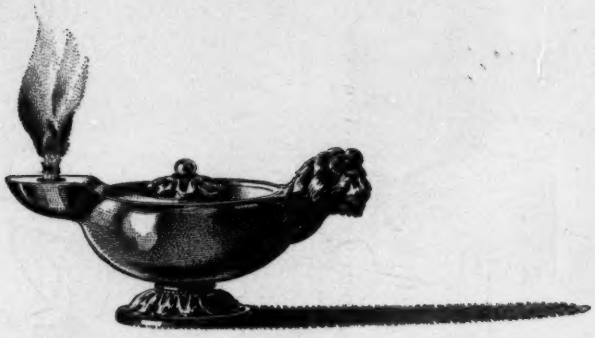
• Each DUOZINE *Dulcet* Tablet contains equal parts of sulfadiazine and sulfamerazine. These drugs, according to a recent report,[1] "... qualify at present for first and second place, respectively, as components of any mixture." The tablets are stable, easy to give in exact dosage. • For children, and adults who prefer sulfonamides sweet, why not try DUOZINE *Dulcet* Tablets? Available at pharmacies in both 0.3-Gm. and 0.15-Gm. potencies, bottles of 100. Abbott

1. Lehr, D. (1950), Relative Merits of Commonly Used Sulfonamide Drugs as Components of Mixtures, N. Y. State J. Med., 50:1361, June.

PRESCRIBE Duozine® TRADE MARK Dulcet® Tablets

(DIA-MER-SULFONAMIDES, ABBOTT)

®MEDICATED SUGAR TABLETS, ABBOTT



"Truth never grows old" *Thomas Fuller, 1639*

With passing years, ideas, theories and conceptions may change with new discoveries and growing knowledge.

But truth never grows old.

No matter how widely the pendulum may swing, *truth* remains the center of its path.

Because of its inherent soundness, Dextri-Maltose® is the carbohydrate of choice in more hospitals than ever before. It enjoys the confidence of ever-growing thousands of physicians.

And the physician who prescribes Dextri-Maltose in infant feeding follows a course confirmed by a great mass of evidence, for no other carbohydrate enjoys so rich and enduring a background of authoritative clinical experience.

However the pendulum may swing, facts remain facts and truth never grows old.

MEAD'S

MEAD JOHNSON & CO.
EVANSVILLE 21, IND., U. S. A.

INTEREST IN AVEENO IS STEADILY MOUNTING

Because

AVEENO provides a soothing demulcent colloid bath that protects tender skin.

Because

AVEENO affords efficient cleansing action without irritation . . . soapless . . soothing.

Because

AVEENO has a pH approximating that of normal skin (about pH 5.5) —thus protecting the natural acid mantle of the skin.

AVEENO
THE NEW
CONCENTRATE
FROM OATMEAL
IS INSTANTLY READY
FOR USE . . . *NO BOILING*
. . . *NO STRAINING*

Because

AVEENO is completely harmless and non-toxic—in fact it is a pure, edible concentrate from fine oatmeal.

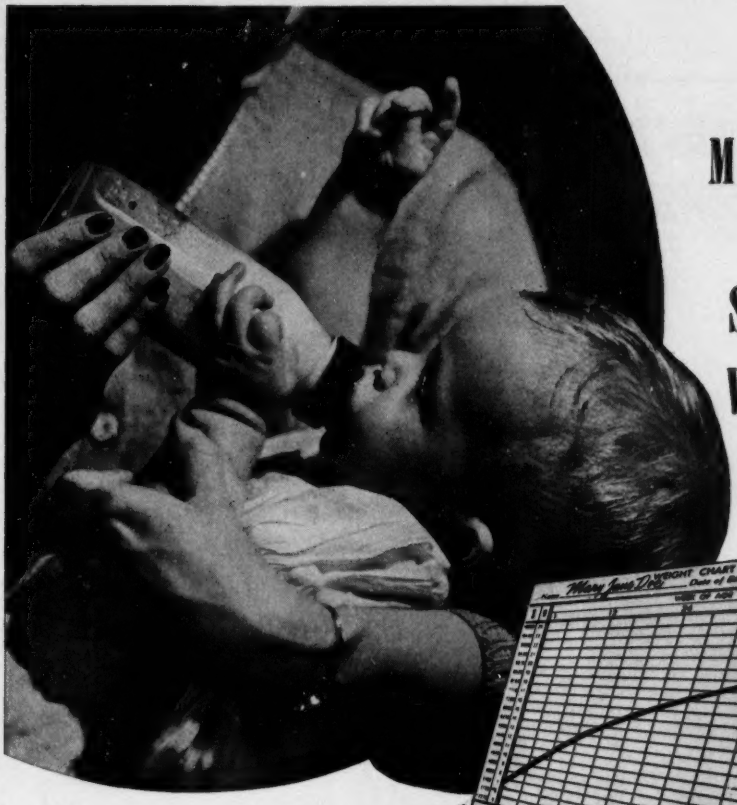
SEND FOR PROFESSIONAL SAMPLES AND LITERATURE.

E. FOUGERA & CO. INC. • Sole Distributors • 75 Varick Street, New York 13, N. Y.

AVEENO . . . *the new concentrate from oatmeal, ready-to-use . . . product of Quaker Oats Company*

AVAILABLE IN DRUG STORES ONLY, IN 18 OZ AND 5 LB PACKAGES

To Maintain a Steady Weight Curve



Cartose is a carefully proportioned mixture of dextrins, maltose and dextrose.

Since each of these carbohydrates has a different rate of assimilation, a steady supply of carbohydrate is released for "spaced" absorption.

Low rate of fermentation.

Low incidence of digestive disturbances.

Bottles of 1 U. S. pint.

Write for formula blanks.

Specifically Designed for Infant Feeding

CARTOSE®

MIXED CARBOHYDRATES IN EASY-TO-USE LIQUID FORM

Compatible with all milk formulas

Less Colic · Less Diarrhea

Winthrop-Stearns INC. • NEW YORK 13, N. Y. WINDSOR, ONT.

Cartose, trademark reg. U. S. & Canada